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535, 537	In title :	*for* " XIX " *read* " XX ".

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384	9	*for* " 147·5 " *read* " 137·5 ".
	27	*for* " 200 " *read* " 220 ".

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173	2 after summary :	*for* " diazo- " *read* " diazo-oxide ".
226	13	*for* " 120 " *read* " 129 ".
244	28*	*for* " B.P. 248,282 " *read* " B.P. 248,182 ".
247	32	*for* " bis-(*m*-diethyl- " *read* " bis-(*m*-dimethyl- ".
247	last	*for* " This " *read* " The acetate of ".
249	28	*for* " -1 : 3- " *read* " -2 : 4- ".
249	38	*for* " 1 : 3- " *read* " 2 : 4- ".
330	43	*for* " 170 " *read* " 182 ".
398	30	*for* " C_{19} " *read* " C_{18} ".
	14*	*for* " 6·1 " *read* " 5·7 ".
767	23*	*after* " complete " *insert* " , at 100°,".
850	13*	*for* " 18·5 " *read* " 8·5 ".

* From bottom.

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Some thirty authors have contributed to this book. Many of them are well known for their original contributions in the fields of biochemistry or food technology. They come from laboratories at academic centres, at government research institutions and at food factories. The book thus represents a piece of scientific collaboration by experts selected without any consideration other than their ability to assemble information and give it accurate expression. The authors have brought together all the knowledge at present available about the composition of the foods, and therefore the diets, of the British people. This has involved a detailed examination of seven main foods or groups of foods and the recording of innumerable data giving their chemical compositions.

The widest possible view has been taken as to the meaning of the words "chemical composition"; besides including vitamins, amino-acids and other constituents of less clear function (nucleo-tides, nitrogenous bases and so on), authors have given attention to the physical properties of the foods and also to the effect on them of cooking and processing. Based on a series of lectures given in war-time Britain, the seven parts of this book have much more than an ephemeral value.

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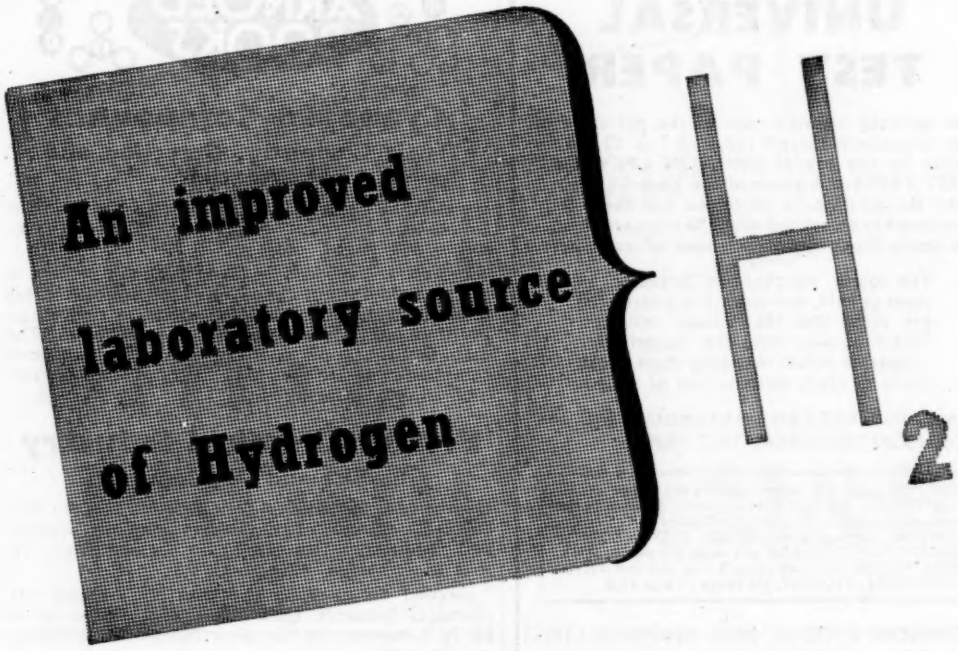

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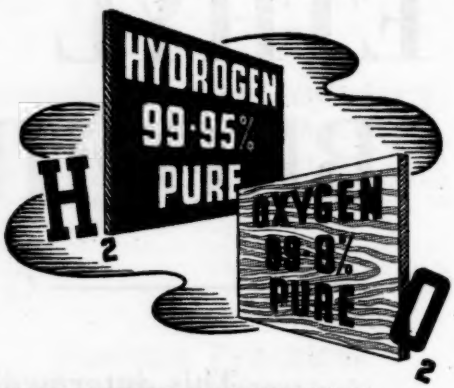

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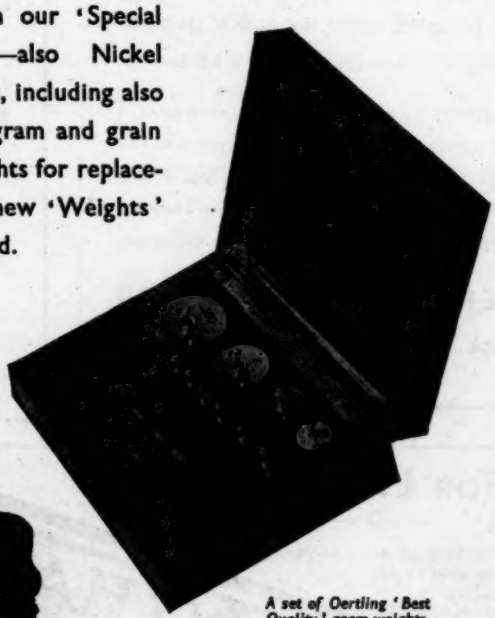

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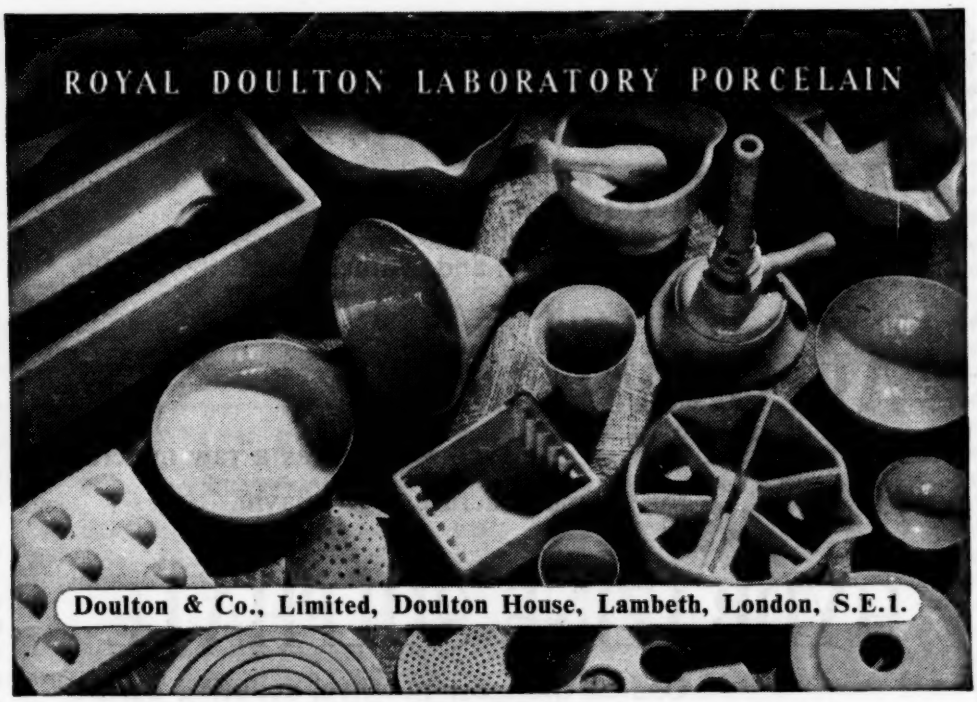

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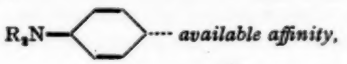
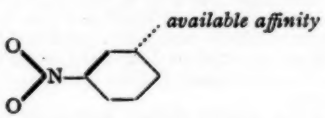
enoid and catio-enoid systems as well as those in which both are present and may be partly neutralised. The direction of the mesomeric displacement was not necessarily in the same sense as the dipole. Thus the dipole in chlorobenzene was in the direction Cl← as the theory of the general effect demands. A small counteracting mesomeric effect Cl→ was detected by comparison of the moment of chlorobenzene with that of *tert.*-butyl chloride (*Proc. Roy. Soc.*, 1931, **133**, 668). This work was a remarkable physical confirmation of the validity of the hypotheses which have briefly been expounded, for it was found that all *op*-directive groups examined increased the density of electrons in the aromatic nucleus and all *m*-directive groups decreased it. Methods for determining the occurrence and extent of mesomerism have been developed by Pauling and others, but they belong to the modern period. The device of writing down the possible structures and estimating the contribution which each makes to the actual condition of the molecule is a calculus and not a theory of structure, though it has often been misunderstood as such.

Conclusion.—Many important tributaries have been omitted from this account and the river has not been followed to the sea. Thus the work of Claus, Werner, and Flürscheim had a most important influence on the thoughts of chemists. Flürscheim's development of the theory of alternating and variable affinity was especially valuable. It gave the results now regarded as correct in many cases, as in the hetero-enoid systems:



but failed to meet our requirements in the catio-enoid systems:



The speculations of Vorländer and Fry likewise contained useful detailed suggestions but were eventually seen to be out of the direct line of progress. The lecturer has perforce had to omit all reference to the stereochemical aspects, such as the Mills–Nixon effect, to W. Baker's applications of chelation, to tautomerism, dissociating systems, and molecular rearrangement, as well as to many other topics of great interest. In particular he has not mentioned the neutral free radicals and atoms, which can be anionoid, *or* cationoid, *or* homopolar.

It seems peculiarly appropriate that a Faraday Lecture should deal with molecular electrical phenomena, although they are of a very simple kind, in relation to properties of the derivatives of benzene, a substance which Faraday discovered. We owe to him the first studies of dielectrics and as a twig from this tree we take the measurement of dipole moments. Above all he was a great electrochemist and was convinced that electricity and chemical affinity could be identified. His Laws of Electrolysis, considered from the point of view of atoms and ions, bear much the same relation to the atomic theory of electricity that the Law of Multiple Proportions bears to the atomic theory of the elements.

In the Faraday Lecture of 1881, Helmholtz said: " Now the most startling result of Faraday's Law is perhaps this. If we accept the hypothesis that the elementary substances are composed of atoms, we cannot avoid concluding that electricity also, positive as well as negative, is divided into definite elementary portions which behave like atoms of electricity ".

The logic is inescapable and yet we must admire the acumen and courage of the remark.

Without forgetting the work of Volta, Davy, and Berzelius, and of many other real pioneers in the middle and later periods, we are right to honour the memory of Michael Faraday, the most illustrious of the founders of a science of electrochemistry.

239. *Theory of Chromatography. Part II.* Chromatograms of a Single Solute.*

By E. GLUECKAUF.

Chromatograms of single solutes, in particular the case of sigmoid isotherms, are treated theoretically and measured experimentally. The form of the chromatograms resulting from the different isotherms and the movement of their characteristic points are shown and calculated (see Figs. 1—6). Adsorption and exchange isotherms can be calculated from chromatographic elution curves (see Figs. 7 and 9). Comparison of an isotherm, determined in this way, with directly determined equilibrium values shows a good agreement (see Fig. 5), and the chromatographic method gives a much larger number of points for less experimental work.

Symbols:

c, concentration in milliequivs. per c.c.
$q = f_{(c)}$, amount of solute taken up by 1 g. of adsorbent (including pore space) in equilibrium with c (m.-equiv./g.).
$f^*_{(c)} = q - ac$, the amount actually adsorbed on the adsorbent.
a, pore space per g. of adsorbent (c.c./g.).
v, volume of developing solution used (c.c.).
v^0, c^0, q^0, volume and concentration of original solution, and amount adsorbed per g. in equilibrium with c^0.
x, distance from the top of the column, measured in g. of adsorbent.
$m = v^0c^0$, amount of solute used (m.-equivs.).
$\mu_{\bar{c}}$, amount of solute in the column behind a given point $\bar{x}$ of concentration $\bar{c}$ on the rear boundary.
$\mu_{\tilde{c}}'$, amount of solute in front of a given point $\tilde{x}$ of concentration $\tilde{c}$ on the front boundary.

Indices in italics refer to characteristic points of the chromatogram, shown in the diagrams:

u to the undeveloped front (*see* Fig. 2, A, B).
w to the front of a fully developed chromatogram (*see* Figs. 2, C and 6, D).
s to the sharp undeveloped rear boundary (*see* Fig. 4, A).
r to the sharp rear boundary of a fully developed band (*see* Fig. 4, B).
o to the point of concentration 0 in a diffuse boundary (*see* Figs. 2, 4, 6).
d to the point of concentration c^0, q^0 in a diffuse boundary (*see* Figs. 2, 4, 6).
e, *e'*, *f*, and ϵ are used for points on a partially diffuse boundary (*see* Fig. 6).

(a) *Chromatographic Equations for Single Solute Isotherms.*—Chromatography is the name given to the process of separation by continuous fractional adsorption, because of its earlier applications to the separations of coloured substances, though this limitation no longer obtains. The normal procedure is to pour a solution of the solutes to be separated on to the top of a column filled with adsorbent and allow it to percolate into the column, a process which may be accelerated by applying suction at the bottom or, better, pressure at the top. After this original solution is taken up by the column, and has formed a band, further amounts of pure solvent are added at the top, dissolving the band of absorbed solutes from the rear and slowly carrying it through the column, a process called "development." During the development stage the band usually spreads, whereby its local concentration decreases and, as the individual solutes move with different speed through the column, partial or complete separation takes place.

The regions in the front and rear of the adsorption band are called "boundaries," and these may be "sharp" or "diffuse" according to the type of adsorption isotherm obtaining for the particular case of adsorbent, adsorbate, and solvent. (The boundaries are always diffuse if the flow of solvent is too fast to permit local equilibrium to be reached; see Part IV.) In thecase of multiple solutes the word "boundary" is applied to all parts where concentration gradients exist.

The movement of any type of boundary is governed by the principle of mass-conservation, which means that, if we consider the solute content of a very thin section of the chromatographic band, its increase (or decrease) is given by the difference of the inflowing and the outflowing solute.

The movement of the band can be considered in two ways.

We can mentally fix our eyes on a given particle of the solute. Then this point of fixed mass within the band of a single solute, the concentration of which may, *e.g.*, be c^0, moves with a given amount of solvent v according to (1) (see Wilson, *J. Amer. Chem. Soc.*, 1940, **62**, 1583):

$$[\Delta x/\Delta v]_m = c^0/f_{(c^0)} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

Alternatively, we may follow the movement of a point of constant concentration in a diffuse boundary (see Fig. 2, C, curve A—B), which is described by equation (2) (see De Vault, *ibid.*, 1943, **65**, 532; Weiss, *J.*, 1943, 297):

$$[\Delta x/\Delta v]_c = dc/df_{(c)} = 1/f'_{(c)} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

* For Part I, see *Proc. Roy. Soc.*, 1946, *A*, **186**, 35.

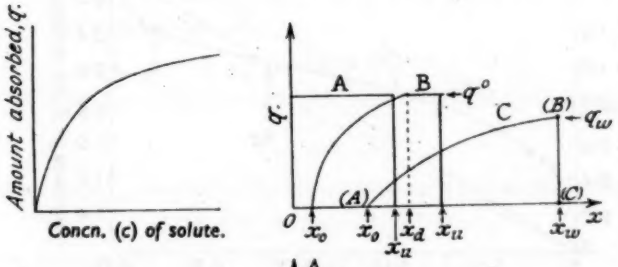
Finally, we have the integrated equations for the amount of solute in the chromatogram between the concentrations $\bar{c}$ and $c = 0$, which in the case of a diffuse rear boundary (see Fig. 2) is

$$\mu = \bar{x}f_{(\bar{c})} - v\bar{c} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

(Glueckauf, *Nature*, 1945, **156**, 748) and for a diffuse front boundary (see Fig. 4) :

$$\mu' = (v + v^0)\bar{c} - \bar{x}f_{(\bar{c})} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

FIG. 1. FIG. 2.



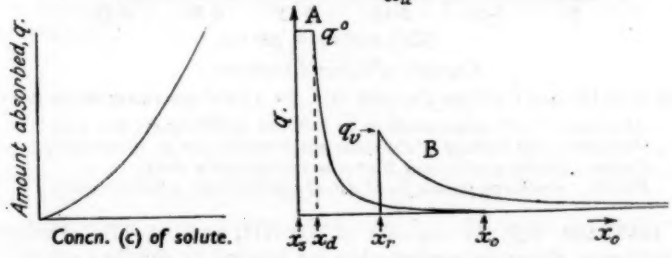


FIG. 3. FIG. 4.

FIG. 1.—*Normal isotherm concave against* c*-axis.*

FIG. 2.—*Development of a band of solute with isotherm as in Fig.* 1.
Abscissa = distance from top of column.
Ordinate = amount absorbed per g. of column material.
(A) *Original band.* (B) *Incomplete development.* (C) *Complete development.* *(A)–(B) Diffuse rear boundary, (B)–(C) sharp front boundary.*

FIG. 3.—*Isotherm convex against* c*-axis.*

FIG. 4.—*Development of a band of solute with isotherm as in Fig.* 3.
(A) *Original band.* (B) *Complete development.*

Equation (3) actually comprises equation (1).

The combinations of these equations represent all the relevant conditions of the various parts of the chromatograms (some of which have already been given by Weiss, *loc. cit*).

For an adsorption isotherm concave towards the *c*-axis (see Fig. 1) we get (for subscripts see Figs. 2, A, B, C) :

$$x_0 = v/f'_{(0)} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5a)$$

$$x_d = v/f'_{(c^0)} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6a)$$

$$x_u = (v + v^0)c^0/f_{(c^0)} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7a)$$

$$x_w = m/(f_{(c_w)} - c_w f'_{(c_w)}) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8a)$$

where c_w is defined by

$$v = mf'_{(c_w)}/(f_{(c_w)} - c_w f'_{(c_w)}) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (9a)$$

For an adsorption isotherm convex towards the *c*-axis (see Fig. 3) we get (for subscripts see Figs. 4, A, B) :

$$x_0 = (v + v^0)/f'_{(0)} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5b)$$

$$x_d = (v + v^0)/f'_{(c^0)} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6b)$$

$$x_s = vc^0/f_{(c^0)} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7b)$$

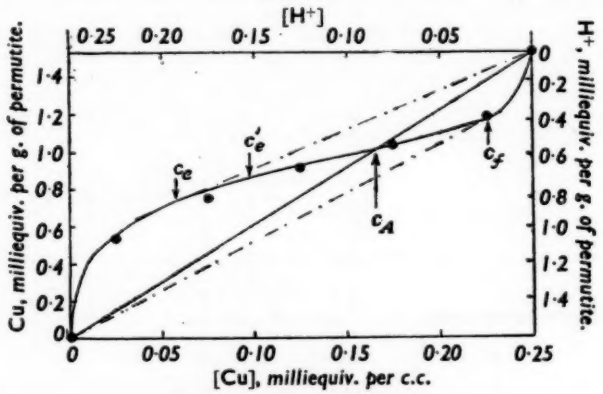
$$x_r = m/(c_r f'_{(c_r)} - f_{(c_r)}) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8b)$$

where c_r is defined by

$$v + v^0 = mf'_{(c_r)}/(c_r f'_{(c_r)} - f_{(c_r)}) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (9b)$$

Slightly more complicated are the conditions in the case of sigmoid isotherms. These are particularly frequent in ion-exchange systems on zeolites, permutites, and exchange resins, in cases where both ions are taken up with similar affinity (see, *e.g.*, Rothmund and Kornfeld,

FIG. 5.

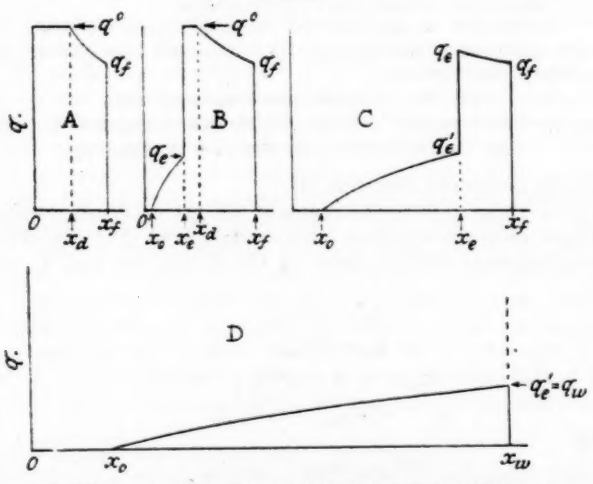


Example of sigmoid isotherm.

Exchange isotherm of H^+ *and* Cu^{++} *on Zeo-carb H.I. for a total concentration in solution of* 0·25N.
Abscissa : Cu^{++} *concentration in solution (milli-equiv. per c.c.).*
Ordinate : Cu *content of zeo-carb (milli-equiv. per g. of zeo-carb).*
Curve : isotherm obtained from chromatographic data.
Points : isotherm points from direct equilibrium measurements.

Z. anorg. Chem., 1918, **103**, 129, for the case of Na–NH_4 and Ag–Tl). Though two ions are involved in any isotherm, they can nevertheless be treated as simple systems, for, under the conditions of constant total concentration existing during the elution process, there is only

FIG. 6.



Development of a band of solute with sigmoid isotherm.

(A) *Original band.*
(B) *Development incomplete.*
(C) *First stage of development completed.*
(D) *Complete development.*

one freely variable concentration. Bands in every respect identical with those produced by adsorption phenomena are obtained by using a solution of the original cation of the permutite as developing agent.

In the case of sigmoid isotherms, chromatograms are obtained which, at first, have partly diffuse and partly sharp boundaries both in front and rear. In the later stages of the develop-

ment, however, their form changes to one of the cases treated above, according to the curvature of the isotherm at low concentrations.

If the isotherm is concave towards the c-axis at low concentration (see Fig. 5), which is usual in exchange equilibria on permutites, the original band after formation has a form shown in Fig. 6A, assuming the form of Fig. 6B after development.

The frontal concentration c_f shown in Fig. 6A, B, C, is defined by the two conditions of movement for the front boundary:

$$[x_f]_{c_f \text{ const.}} = (v + v^0)/\mathrm{f}'_{(c_f)} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (10)$$

(see equation 1) for the diffuse edge, and

$$[x_f]_{\mu=0} = c_f(v + v^0)/\mathrm{f}_{(c_f)} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (11)$$

(see equation 1 or 7) for the sharp front. The combination of these two equations leads to the condition for c_f:

$$\mathrm{f}'_{(c_f)} = \mathrm{f}_{(c_f)}/c_f \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (12)$$

The rear concentration c_e is defined by the conditions of mass conservation:

$$v/x = \Delta \mathrm{f}_{(c)}/\Delta c = (\mathrm{f}_{(c^0)} - \mathrm{f}_{(c_e)})/(c^0 - c_e) \quad . \quad . \quad . \quad . \quad . \quad . \quad (13)$$

(corresponding to equation 1), and by the movement of a point of the diffuse rear boundary of constant concentration c_e:

$$v/x = \mathrm{f}'_{(c_e)} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2')$$

resulting in

$$\mathrm{f}'_{(c_e)} = (\mathrm{f}_{(c^0)} - \mathrm{f}_{(c_e)})/(c^0 - c_e) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (14)$$

It follows from (12) and (14) that the concentrations c_e and c_f can be obtained very simply from the adsorption isotherms. They represent the points where the tangents from the points $c = 0$ and $c = c^0$ touch the adsorption isotherm (see Fig. 5).

The first stage of development, when the original concentration c^0 disappears, is completed when x_e overtakes x_d. Thus

$$v_{d,e} = v^0 \mathrm{f}'_{(c_e)}/(\mathrm{f}'_{(c^0)} - \mathrm{f}'_{(c_e)}) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (15)$$

With further development the diffuse rear band continues to increase in quantity at the expense of the rest. With the fall of c_e (see Fig. 6C) is connected a slow rise of c'_e. When x_e catches up with x_f (see Fig. 6D), c'_e is given by the condition

$$\mathrm{f}'_{(c'_e)} = (\mathrm{f}_{(c_f)} - \mathrm{f}_{(c'_e)})/(c_f - c'_e) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (16)$$

From this point onwards the chromatogram behaves like a fully developed band in case (*a*), and equations (2), (2*a*), (3), (4*a*), and (4*b*) apply. The position of the band at this point is given by (4*a*) and (4*b*) with $c_w = c'_e$. If the isotherm is known, c'_e can be obtained by drawing a tangent (not shown in Fig. 5) from c_f which touches the isotherm in c'_e.

In the case of sigmoid isotherms which are concave at low concentrations (as found for some dyes in aqueous solution when adsorbed on alumina), similar conditions arise but with the bands in a reversed position.

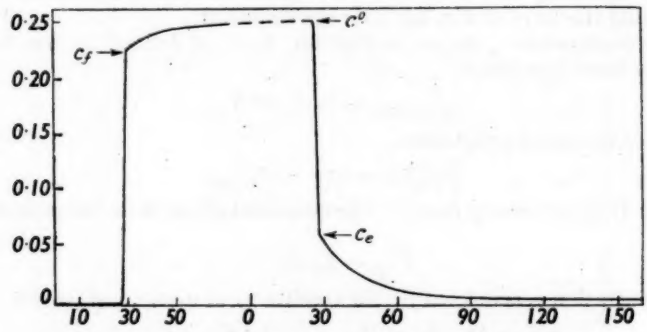
An interesting feature attaches to the point c_A of the exchange isotherm (see Fig. 5), where the latter is intersected by the diagonal of the phase rectangle. At this point $c_1/c_2 = q_1/q_2$ and, consequently, this composition shows all the characteristics of an azeotropic mixture. This has the result that if, *e.g.*, a solution of 0·165N-$CuSO_4$ + 0·085N-H_2SO_4 is poured on Na-Zeo-karb H.I., no separation of either copper sulphate or sulphuric acid takes place at the front boundary until full development has taken place.

(b) *Determination of Sigmoid Adsorption Isotherms from Chromatographic Data.*—It is apparent that, in both types of sigmoid isotherms, the chromatogram nowhere contains concentrations between c'_e and c_f, so in this case it is not possible to calculate the whole of the adsorption isotherm from a single chromatographic experiment. Fig. 7 shows the concentrations in the eluate obtained when 0·25N-$CuSO_4$ solution is passed through a column containing 5 g. of acid Zeo-karb H.I. and subsequently eluted with 0·25N-HCl.

The elution curves were registered automatically by measuring the conductivity of the solutions with a recording microammeter. The arrangements of the circuit used are shown in Fig. 8. The only operations necessary were occasional measurements of the quantity of eluate, so as to correlate it with the time scale of the recording instrument, and the determination of the end concentration and of the residual cupric or hydrogen ion in the column at the end of the elution process when the concentrations had become too low to be measured accurately with

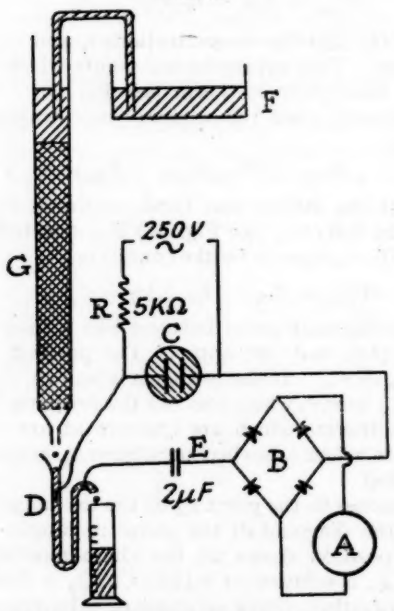
the recorder. (The residual cupric ion was eluted with 2N-H_2SO_4, which removed it quickly, and then titrated.) To avoid non-equilibrium phenomena, the permutite material was ground to a grain size of 0·02 mm. diameter.

FIG. 7.



Measured elution curve of a solute with sigmoid isotherm.
Abscissa: volume of eluate (c.c.).
Ordinate: concentration of eluate, milliequiv./c.c.
(Compare with the band shown in Fig. 6B.)

FIG. 8.



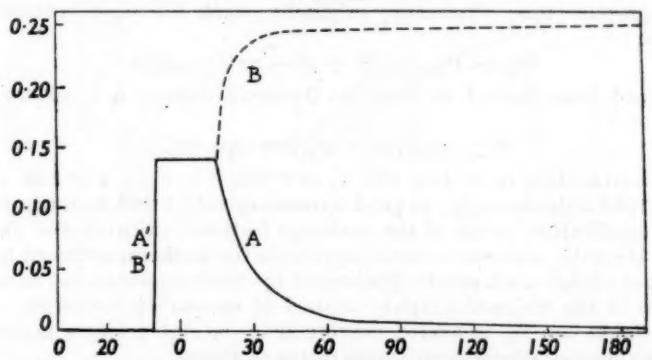
Arrangement for the automatic registration of concentrations in the eluate.
(A) *Recording μ-ammeter* (0—100 μA.)
(B) *Full-wave rectifier.*
(C) *Neon voltage-stabiliser.*
(D) *Capillary with Pt electrodes for resistance measurement of eluate.*
(E) *Condenser* 2μ F.
(F) *Constant level for constant dropping speed.*
(G) *Column filled with 5 g. of Zeo-carb.*
(R) 5000 Ω *resistance.*

The eluate consists at first of 0·25N-H_2SO_4. The front of the copper arrives at a threshold volume $v_t = 29$ c.c. Its concentration rises sharply to a value of $c_f = 0{\cdot}225$, as one would expect from the theory (eqn. 12) which fixes this concentration as the point where the tangent from the origin ($c = 0$), touches the isotherm (see Fig. 5). Thence the concentration rises asymptotically to the original value $c^0 = 0{\cdot}25$ milliequiv./c.c.

After passing a sufficiently large amount of copper solution through the column to convert the zeo-karb completely into Cu-zeo-karb, this "undeveloped band" was now "developed" with 0·25N-H_2SO_4, whereby the rear boundary of the copper band was obtained. Here, too, the concentration fell at first sharply to a value of $c_e = 0{\cdot}060$ milli-equiv./c.c. [which again is in agreement with the theory (eqn. 14), representing the point in Fig. 5 where the tangent from the point $c^0 = 0{\cdot}25$ milliequiv./c.c. touches the exchange isotherm]. With continued elution, the copper concentration exhibits the normal behaviour and falls asymptotically to zero (see Fig. 7).

Thus the greater part of the isotherm, between $c_e = 0{\cdot}060$ and $c_f = 0{\cdot}225$, cannot be calculated from the chromatographic data of this experiment, as these concentrations do not appear in the chromatogram. Boundaries covering the whole concentration range can, however, be obtained by saturating the column with solute of the concentration (c_i) existing at the point of inflexion (or near by), and then (i) eluting with pure solvent (acid) and (ii) saturating the column with the concentration c^0. From the first experiment (elution of a copper band) results a diffuse rear boundary which permits the calculation of the adsorption data between c_i and 0; in the second case (elution of an acid band) is obtained a diffuse boundary between c_i and c^0.

FIG. 9.



Measured "elution curves" of a solute with sigmoid isotherm, suitable for determination of the isotherm by means of eqn. (3) *or* (4).

TABLE I.

(From curve A, Fig. 9.)

v (obs.).	c (obs.).	$\Delta\mu$.	μ.	$(v - ax)c$.	$xf^*_{(c)}$.	$f^*_{(c)}$.
$14{\cdot}5 = V_i$	0·140		3·62	1·19	4·81	0·962
		0·56				
19·1	0·103		3·06	1·35	4·41	0·882
		0·49				
24·9	0·066		2·57	1·25	3·82	0·764
		0·31				
30·6	0·044		2·26	1·08	3·34	0·668
		0·22				
36·4	0·033		2·04	1·00	3·04	0·608
		0·17				
42·1	0·028		1·87	1·01	2·88	0·576
		0·40				
63·1	*0·010*		*1·47*	0·57	2·04	0·408
166	*0·005*		*0·73*	0·80	1·53	0·306

TABLE II.

(From curve B, Fig. 9).

$v + v^0$.	c.	$\Delta\mu$.	μ.	$(v + v^0 - ax)c$.	$xf^*_{(c)}$.	$f^*_{(c)}$.
$15{\cdot}3 = V$	0·140		*2·14*	1·30	4·81	*0·962*
		0·18				
16·5	0·166		2·32	1·74	5·08	1·016
		0·37				
18·5	0·200		2·68	2·50	5·47	1·094
		0·41				
2·04	0·213		3·07	3·07	5·65	1·130
		1·17				
25·6	0·227		4·19	4·45	5·91	1·182
		2·04				
34·0	0·237		6·15	6·71	6·21	1·242
∞	0·250		—	—	*7·50*	*1·500*

Italicised values are measured directly. Other values of cols. 1, 2, 3 are taken from the registered elution curves. Col. 6 in Table I is the sum of cols. 4 + 5. Col. 6 in Table II is (5·65 + col. 5 − col. 4). The figure 5·65 represents $(f^*_{(c^0)} + ac^0)x$, *i.e.*, the amount of solute in the column at the time of the change-over. $\Delta\mu$ is the eluate between two evaluated points, *i.e.*, the product of Δv and the average concentration. The amount μ left in the column is obtained by adding all the $\Delta\mu$'s to the amount finally left in the column and measured directly.

In either case no discontinuous "rear" boundaries are obtained, because from this point (c_i) no tangent can be drawn to any other part of the isotherm.

The elution curves shown in Fig. 9 A, B are obtained in the following way: Through a column of acid Zeo-karb (5 g.) was passed a solution of 0·14N-$CuSO_4$ + 0·11N-H_2SO_4 which approximately corresponds to the mixture at the point of inflexion of the isotherm. The copper arrived in the eluate with a sharp front boundary ($v_t = 40$ c.c.). Then the solution was changed, 0·25N-H_2SO_4 (see curve A) being used for the elution of the copper, and (see curve B) in a second experiment 0·25N-$CuSO_4$ for the elution of the hydrogen ions. In either case a diffuse rear boundary was obtained beginning at about 14·5 and 15·3 c.c. respectively after the change-over.

From these two curves the complete exchange isotherm can be calculated. Curve A can be evaluated according to eqn. (3):

$$f^*_{(\bar{c})} = [\mu_{\bar{c}} + (v - \alpha x)\bar{c}]/x \text{ (see Table I).}$$

Curve B can be evaluated in two ways: It can be considered as the rear boundary of a hydrogen-ion band, and then eqn. (3) applies, with c referring to the hydrogen-ion concentrations. Alternatively, it can be considered as the partial front of a pure copper-ion band moving against a mixed solution, in which case eqn. (4) applies [though with some modification on account of the chromatographic tube containing originally some Cu (c_0)]. Integration for these conditions leads to:

$$f^*_{(\bar{c})} = f^*_{(c_0)} + [(v + v^0 - \alpha x)\bar{c} - \mu_{\bar{c}}]/x$$

where $f_{(c_0)}$ is obtained from Table I, or from the threshold volume $v_t = 40$ (frontal line A′B′ of Fig. 9) by means of

$$f^*_{(c_0)} = v_t c_0/x - \alpha c_0 \text{ (see eqn. 1}a\text{).}$$

From the experimental data ($v_t = 40{\cdot}0$ c.c., $c_0 = 0{\cdot}140$, $x = 5$ g., $\alpha = 1{\cdot}20$ c.c./g.) follows a value for $f^*_{(c_0)} = 0{\cdot}953$ milli-equiv./g., in good agreement with 0·962 found from Table I. The agreement of the equilibrium values of the exchange isotherm calculated in Tables I and II is shown in Fig. 5. Here the continuous curve represents the isotherm obtained by the chromatographic method, and circles mark points determined by direct equilibrium measurements. The obvious advantage of the chromatographic method of measuring isotherms, especially if the concentration of eluate can be measured continuously, is that a single experiment gives an almost unlimited number of equilibrium points of the isotherm.

(c) *Gas Adsorption Columns* (added in proof, August, 1947).—The considerations about the distribution of solutes in an adsorption column apply equally to the case of gases adsorbed from an air stream in adsorption columns. In the recently published experimental observations of Barrow, Danby, Davoud, Hinshelwood, and Staveley (this vol., p. 401), the different cases of Figs. 1 and 2, A and of Figs. 3 and 4, A are found when air containing carbon tetrachloride and water vapour respectively is passed through a charcoal column. The removal of the adsorbates from the column by passing clean air through (see their Figs. 7, 8, and 11, 12) corresponds to a development with pure solvent and is represented by Figs. 2B, C and 4B of this paper and by the corresponding equations. The above-mentioned experiments with gases also show clearly the effect of non-equilibrium phenomena, which are more fully discussed in Part IV.

DURHAM COLLEGES IN THE UNIVERSITY OF DURHAM. [*Received, November 20th*, 1946.]

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240. *Theory of Chromatography. Part III. Experimental Separation of Two Solutes and Comparison with Theory.*

By J. I. COATES and E. GLUECKAUF.

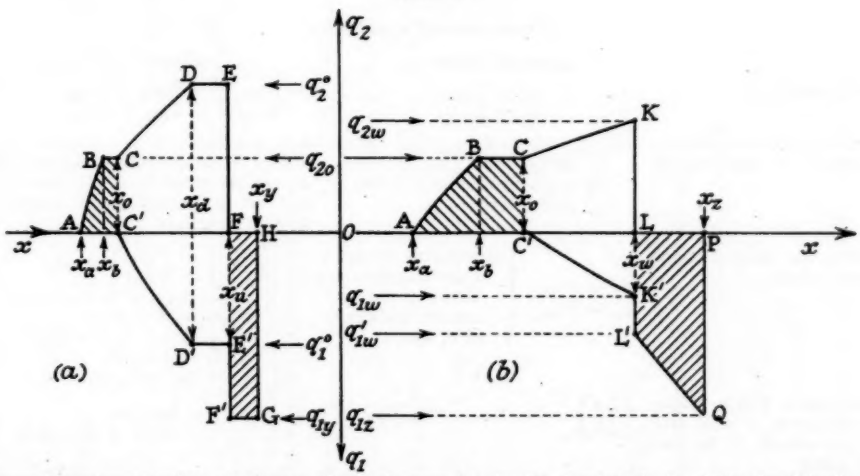
The results obtained in Part I (*Proc. Roy. Soc.*, 1946, *A*, **186**, 35) for chromatograms of two solutes are summarised in Tables I—V, giving the features and movements of the important parts of binary chromatograms (see Fig. 1) at various stages of the development. The results are given both for the general case and for the special case of the Langmuir isotherm.

The agreement of these calculations with quantitative elution experiments is shown for a chromatographic separation of Cu^{++} and Mn^{++} on Zeo-karb H.I. (see Fig. 2, 3, and 4), the exchange of which follows approximately an isotherm of the Langmuir type.

(*a*) *Summary of Part I.*—A normal binary chromatogram has, according to whether it is fully developed or not, a distribution of solutes as shown in Fig. 1*b* and 1*a*, respectively. (Some

modifications may occur if the isotherm has an infinite slope at zero concentrations, as, *e.g.*, in the case of the Freundlich isotherms; see Part V.) The movement of any given point of such a chromatogram can be given in general mathematical terms, but only in the case of the Langmuir isotherm (see eqn. 1) can the essential differential equation (2), defining the relationship of coexistent concentrations c_1 and c_2 in the mixed band, be solved. Once this function is known for a given case of initial concentrations c_1^0 and c_2^0, the adorption isotherm $q_1 = f_1(c_1, c_2)$ can be replaced in the mixed band by the pseudo-isotherm $q_1 = F_1(c_1)$ (eqn. 3), so that the problem is thereby reduced to the case of a single solute isotherm. In this way the difficulty mentioned by de Vault (*J. Amer. Chem. Soc.*, **1943**, **65**, 532) of obtaining the full differential $df_{1(c_1c_2)}/dc_1$ is being solved. The essential data for the development of a binary chromatogram are given in Tables I—V, with full reference to the corresponding parts in Fig. 1*a*, *b*. In these tables, the pore space of the adsorbent has not been considered. Correction for this can be made by

FIG. 1.



Diagrammatic representation of binary chromatogram (a, *partly developed*; b, *fully developed*), *showing the amounts* q_1 *and* q_2 *adsorbed per g. of adsorbent at various distances* x *from the top of the column. The subscripts and figures are referred to in Tables III—VII giving quantitative informaiton on the movements of points and boundaries.*
The pure front band of solute 1 *and the pure rear band of solute* 2 *are hatched.*

substituting $(v - \alpha x)$ for v, or by replacing $f_{(c)}$ by $f_{(c)} + \alpha c$, whichever is more convenient. The equations may be used for the calculation of both chromatograms and elution curves according to whether they are applied to a constant value of v (giving a relation between the " length " x and c) or to a constant value of x, the total adsorbent in the column (giving a relation between the volume of eluate v and its concentration c).

(*b*) *Conclusions of Practical Interest derived from the Equations of Part I for Separation of Two Solutes.*—(1) For the Langmuir type of isotherm, separation is facilitated by working at high adsorption densities, but no advantage is derived from using high solute concentrations when the adsorbent is already fairly saturated.

(2) If this is done, the amount of adsorbent and also the amount of developing solution required for complete separation are proportional to $(m_1 + m_2)$, *i.e.*, to the total quantity of the solutes. A rough practical rule for the minimum amount X_o of adsorbent required for complete separation would be $X_o = L^0/(\Delta x_1/\Delta x_2 - 1)^2$ where L^0 is the amount of adsorbent taken up by the original undeveloped band, and Δx_1 and Δx_2 are the displacements of the rear of the pure single-solute bands produced by equal amounts of developing solvent; Δx can easily be determined if the pure solutes are available. More than the amount X_o is required for a good spatial separation of the bands.

(3) If solutes are so difficult to separate that no complete separation, but only enrichment can be achieved, it is always an advantage to develop with a solution containing a third and more strongly adsorbed solute of at least equal concentration. Here the amount of adsorbent required to separate the solutes is approximately only $X_o = L^0/(\Delta x_1/\Delta x_2 - 1)$ but, as the two bands do not separate, a mixed band always remains on account of non-equilibrium effects

(see Part IV). The displacements Δx_1 and Δx_2 have to be determined in the absence of the third solute. It is obvious that development with a third solute gives the advantage of requiring shorter columns only if $(\Delta x_1/\Delta x_2 - 1) \ll 1$. Other advantages of using a third solute, like the greater mobility in the case of very strongly adsorbed solutes, are independent of this consideration.

Experimental

The experiments were carried out with columns containing 60 g. of acid Zeo-karb H.I. The attainment of equilibrium (see subsequent paper) is of particular importance in the case of chromatography with ion exchangers, for the diffusion in these is somewhat slower than, *e.g.*, in alumina. However, by using a grain size of 0·01 mm. diameter and a flow velocity of 0·001 cm./sec. (corresponding to one drop in two minutes), elution curves were obtained which were even better than those obtainable with the apparently faster alumina of equal grain size. This seems to be due to a different effect altogether. Acid Zeo-karb when taking up larger ions like copper or manganese, undergoes a noticeable

Table I.

Fundamental equations.

	General isotherm.	Langmuir isotherm.
Adsorption isotherm	$q_1 = f_{1(c_1c_2)}$ $q_2 = f_{2(c_1c_2)}$	$q_1 = a_1c_1/(1 + b_1c_1 + b_2c_2)$ $q_2 = a_2c_2/(1 + b_1c_1 + b_2c_2)$ . . . (1)
Condition for coexistent concentrations in the mixed band	$df_{1(c_1c_2)}/dc_1 = df_{2(c_1c_2)}/dc_2$ can be integrated graphically for a given case of c_1^0 and c_2^0 (see Part V)	$a_2b_1c_1 = a_1b_2c_2\lambda - (a_2 - a_1)\lambda/(1 + \lambda)$, where λ can be obtained from the same equation with $c_1 = c_1^0$ and $c_2 = c_2^0$. In the following, λ is considered a known constant . . . . . (2)
Pseudo-adsorption isotherms in mixed band	$q_1 = F_{1(c_1)}$, $q_2 = F_{2(c_2)}$ obtainable from relationship between coexistent values of c_1 and c_2	$q_1 = A_1c_1/(1 + B_1c_1)$, $q_2 = A_2c_2/(1 + B_2c_2)$ where $A_1 = a_1(1 + \lambda)/(1 + \lambda + \delta)$, $B_1 = b_1(1 + \lambda)/\lambda$, $A_2 = a_2(1 + \delta)(1 + \lambda)/(1 + \lambda + \delta)$, $B_2 = b_2(1 + \lambda)$, $\delta = (a_2 - a_1)/a_1$ . . . (3)
Movement of a given mass-point of solute 1 (and *vice versa* for solute 2) in the mixed band	$\left[\frac{\Delta x}{\Delta v}\right]_{m_1} = c_1/f_{1(c_1c_2)} = c_1/F_{1(c_1)}$	$= (1 + b_1c_1 + b_2c_2)/a_1$ $= (1 + B_1c_1)/A_1$. (4)
Movement of point of given concentrations c_1, c_2 in a diffuse boundary	$\left[\frac{\Delta x}{\Delta v}\right]_{c_1c_2} = 1/F'_{1(c_1)} = 1/F'_{2(c_2)}$	$= (1 + B_1c_1)^2/A_1 = (1 + B_2c_2)^2/A_2$ (5)
Amount of solute in the chromatogram between the points of concentrate c and $c = 0$ (c within the mixed band)	$m_{1(0-x)} = xf_{1(c_1c_2)} - vc_1$ $m_{2(0-x)} = xf_{2(c_1c_2)} - vc_2$	Same . . . . . (6

Table II.

Important concentrations in the chromatogram (see Fig. 1*a*, *b*).

	General isotherm.	Langmuir isotherm.
c_{2v}	Obtainable from graphical integration	$c_{2v} = \delta/B_2$ . . . . . (7)
c_{1y}	Obtainable from $\frac{c_{1y} - c_1^0}{c_2^0} = \frac{f_{1(c_{1y})} - f_{1(c_1^0c_2^0)}}{f_{2(c_1^0c_2^0)}}$	$c_{1y} = c_1^0(1 + \lambda)/\lambda$ . . . . . (8) $\simeq c_1^0 + c_2^0 - c_{2v}$
c_{2w}	Obtainable from $v = m_2\frac{F'_{2(c_{2w})}}{F_{2(c_{2w})} - c_{2w}F'_{2(c_{2w})}}$	$c_{2w} = \sqrt{(m_2/B_2v)}$ . . . . . (9)
c_{1w}	Obtainable from c_{2w} by means of the graphically obtained $c_1 - c_2$ relation	$c_{1w} = \lambda(a_1b_2/a_2b_1)c_{2w} - \lambda(a_2 - a_1)/a_2b_1(1 + \lambda)$ (10) $\simeq \lambda(c_{2w} - c_{2v})$
c'_{1w}	Obtainable from c_{1w} by $\frac{c'_{1w} - c_{1w}}{c_{2w}} = \frac{f_{1(c'_{1w})} - F_{1(c_{1w})}}{F_{2(c_{2w})}}$	$c'_{1w} = c_{1w}(1 + \lambda)/\lambda$ . . . . . (11) $\simeq c_{1w} + c_{2w} - c_{2v}$
c_{1s}	Obtainable only by graphical evaluation according to	$\int_{x_0}^{x_2} q_1 dx = m_1$ . . . . . (12)

The corresponding values of q are obtainable from c by means of eqn. (1).

Table III.

Equations for the different chromatographic boundaries (see Fig. 1*a*, *b*).

Type of boundary.	Ref. for Fig. 1 *a*, *b*.	General isotherm.	Langmuir isotherm.
Rear boundary of pure solute 2	$A - B$	$v/x = [\delta f_{2(c_1c_2)}/\delta c_2]_{c_1=0}$	$v/x = a_2/(1 + b_2c_2)^2$ . . . . . (13)
Rear boundary of solute 2 in mixed band (developed)	$C - D$ and $C - K$	$v/x = F'_{2(c_2)}$	$v/x = A_2/(1 + B_2c_2)^2$ . . . . . (14)
Rear boundary of solute 1 in mixed band (developed)	$C' - D'$ and $C' - K'$	$v/x = F'_{1(c_1)}$	$v/x = A_1/(1 + B_1c_1)^2$ . . . . . (15)
Rear boundary of pure solute 1 in fully developed frontal band	$L' - Q$	$x = \frac{v}{f'_{1(c_1)}} + \frac{m_2(f'_{1(c_1)} - F'_{2(c^*_{2w})})}{f'_{1(c_1)}(F_{2(c^*_{2w})} - c_{2w}F'_{2(c^*_{2w})})}$ Where c^*_{2w} is a function of c_1 such that if $c_1 = c'_{1w}$ then c^*_{2w} is the corresponding c_{2w}	$x = v(1 + b_1c_1)^2/a_1 + \delta m_2b_2(1 + b_1c_1)^2/a_1(\delta + b_2c_1)^2$ (16)
Front of mixed band (undeveloped)	$E - F$ $E' - F'$	$x_u = (v + v^0)c_2^0/f_{2(c_1^0c_2^0)}$	$x_u = (v + v^0)(1 + b_1c_1^0 + b_2c_2^0)/a_2$ . . . . . (17)
Front of mixed band (developed	$K - L$ $K' - L'$	$x_w = m_2/(F_{2(c_{2w})} - c_{2w}F'_{2(c_{2w})})$ (*see* c_{2w})	$x_w = [\sqrt{(v/A_2)} + \sqrt{(m_2B_2/A_2)}]^2$ . . . . . (18)
Front of pure solute 1 (undeveloped)	$G - H$	$x_y = (v + v^0)c_{1y}/f_{1(c_{1y})}$ (*see* c_{1y})	$x_y = (v + v^0)(1 + b_1c_{1y})/a_1$ (see c_{1y}) . . . . . (19)
Front of pure solute 1 (developed)	$Q - P$	Graphical solution only (see c_{1z})	— . . . . . (20)

Table IV.

Amount of solute in different parts of the chromatogram.

Part of chromatogram.	Ref. to Fig. 1*a*, *b*.	General isotherm.	Langmuir isotherm.
Pure rear band of solute 2 (developed or undeveloped)	Area $ABCC'$	$v\frac{(F_{2(c_{20})} - c_{20} \cdot F'_{2(c_{20})})}{F'_{2(c_{20})}}$	$v\delta^2/B_2$ . . . . . (21)
Pure front band of solute 1 (undeveloped)	Area $FE'F'GH$	$(v + v^0)c_1^0(1 - c_2^0 \cdot f_{1(c_1^0c_2^0)}/c_1^0 \cdot f_{2(c_1^0c_2^0)})$	$(v + v^0)c_1^0(a_2 - a_1)/a_2$. (22)
Solute 1 in mixed band (developed)	Area $C'K'L$	$v(F_{1(c_{1w})} - c_{1w}F'_{1(c_{1w})})/F'_{1(c_{1w})})$ (see c_{1w})	$B_1vc_1^2w$ (see c_{1w}) . . . (23)

The other parts are obtainable by difference from m_1 or m_2.

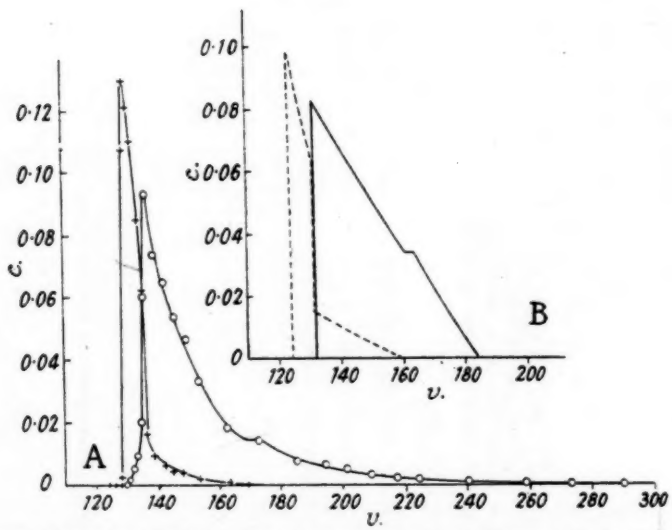
TABLE V.

Conditions for complete separation.

	General isotherm.	Langmuir isotherm.	
Minimum amount of adsorbent required	$X_0 = m_2/(F_{2(c_{20})} - c_{20}F'_{2(c_{20})})$	$X_0 = m_2B_2/A_1\delta^2 \approx (m_1 + m_2)b_2/a_1\delta^2$	(24)
Minimum volume of developing solvent required	$V = m_2/(F_{2(c_{20})})/F'_{2(c_{20})} - c_{20})$	$V = m_2B_2/\delta^2 \approx (m_1 + m_2)b_2/\delta^2$	(25)

swelling, which has a stabilising effect on the front boundary of the ion band. For instance, if one side of the boundary should get in advance of the rest, the flow resistance on this side increases on account of the swelling, so that the other parts of the boundary can catch up. The effect is so marked that an ion band can be passed through a 1 m. column of 1" diameter, without showing a noticeable tilt in the circular front boundary.

FIG. 2.



Eluted chromatogram (fully developed) for partial separation of (1) Mn^{++} *and* (2) Cu^{++} *on* 60 *g. of Zeo-karb H.I. Development with* 1N-H_2SO_4. *Experimental conditions:* $m_1 = 0{\cdot}6$ *milliequiv.,* $m_2 = 2{\cdot}0$ *milliequivs.,* $c_1^0 = 0{\cdot}1$N, $c_2^0 = 0{\cdot}4$N. *Isotherm constants:* $a_1 = 2{\cdot}12$, $b_1 = 2{\cdot}3$, $a_2 = 2{\cdot}35$, $b_2 = 2{\cdot}56$. $\alpha = 0{\cdot}7$ *c.c./g. Grain size of Zeo-karb* 0·01 *mm. Flow velocity* ~100 *c.c./24 hours. Note the exceedingly sharp front boundary due to reduction of non-equilibrium phenomena.*
(*B*) *Elution curve calculated with the equations of Tables I—III for a Langmuir isotherm with the above constants.*

The columns used had a diameter of 1 cm. and were filled with suspended acid Zeo-karb H.I., the usual method of tapping and stuffing being employed. Equally good results were obtained if the tubes were filled with large quantities of material at a time, these being allowed to settle while the whole tube was subjected to constant vigorous vibrations by means of a bell movement clamped to the tube. This method saves much labour with large tubes and produces a very uniform sedimentation of the particles.

The elution curves were obtained by collecting, with an automatic device, fractions of the eluted solution, and analysing these by titration. Within the limits of the analytical error, the recovery of the solutes from 60 g. of Zeo-karb appeared to be 100%, but varying losses were obtained when working with alumina (see also Jacobs and Tompkins, *Trans. Faraday Soc.*, 1945, **41**, 403, Fig. 4).

Results.—Considerable difficulty was experienced in finding a binary system which follows a Langmuir isotherm (see eqn. 1). The nearest approach was found in the exchange isotherms of cupric, manganese, and hydrogen ions on exchange resins (Zeo-carb H.I. and H.I.P) for 1N. and higher total concentrations, and then only when more than 50% of hydrogen ions were present. For a lower hydrogen-ion ratio, the isotherm attains a sigmoid form, and for lower total concentration it changes increasingly towards the Freundlich type (see Part II, Fig. 5). However, within the region of

$$[Cu] + [Mn] < [H]$$

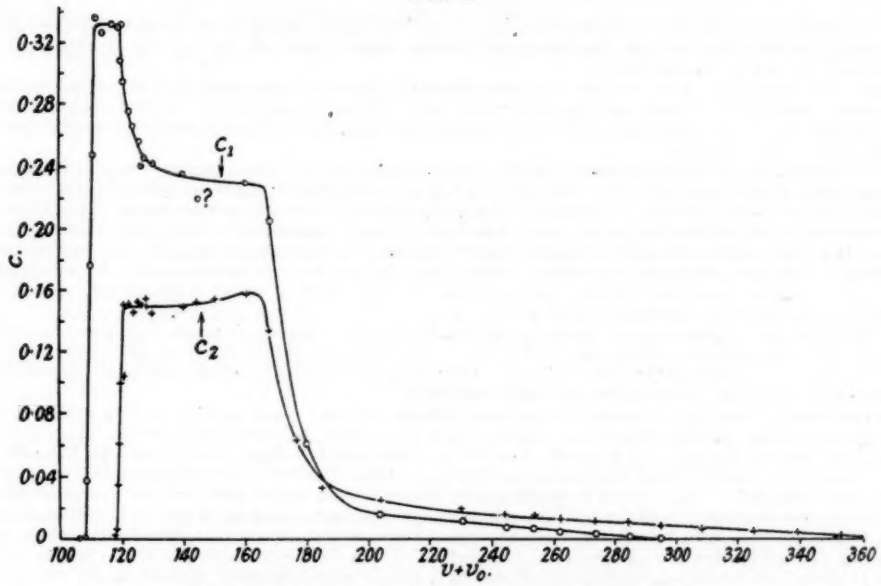
and

$$[Cu] + [Mn] + [H] = 1 \text{ milliequiv./c.c.} \quad . \quad . \quad . \quad . \quad . \quad (26)$$

the exchange isotherm can be well represented over the greater part of its course by equations of the type

$$q_{Mn} = q_1 = K_1[Mn]/([H] + K_3[Mn] + K_4[Cu]) \quad . \quad . \quad . \quad . \quad . \quad (27)$$

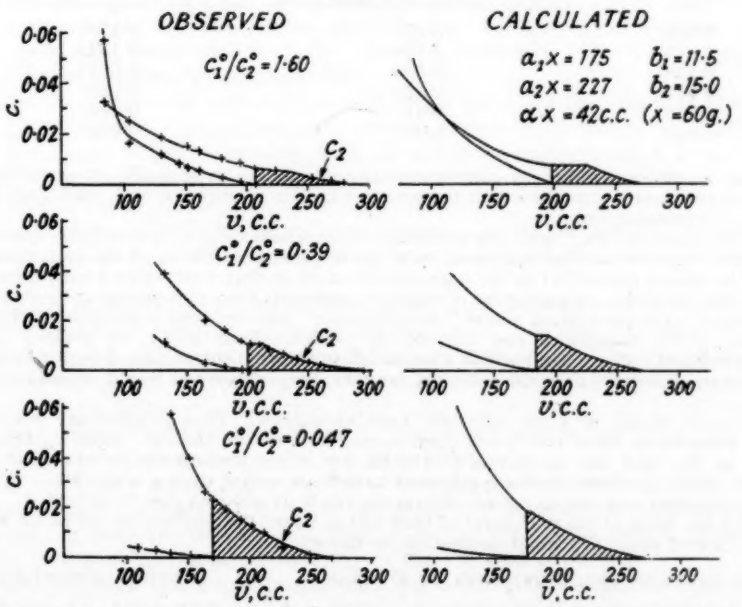
FIG. 3.



Elution curve for two solutes (development incomplete.)

Eluted chromatogram ("development" incomplete) of (1) Mn^{++} *and* (2) Cu^{++} *on* 60 *g. acid Zeo-karb H.I. Development with* 1N-H_2SO_4. $c_1^0 = 0{\cdot}23$N, $c_2^0 = 0{\cdot}16$N.

FIG. 4.



Observed and calculated rear boundary effects for different ratios of the initial concentrations c_1^0/c_2^0. *Note that the form of and amount separated in the pure rear band depends on* c_1^0/c_2^0. *Calculation acc. to Tables I—IV.*

and *vice versa* for q_{Cu}. Eliminating [H] by means of the condition of constant total concentration (eqn. 26) we obtain Cu–Mn isotherms

$$q_{Mn} = K_1[Mn]/\{1 + (K_2 - 1)[Mn] + (K_4 - 1)[Cu]\} \quad . \; . \; . \quad 28)$$

and similarly for q_{Cu}. These equations are formally identical with the Langmuir isotherm (eqn. 1).

At the very lowest metal concentrations [$(c_1 + c_2) < 0{\cdot}03$N], rather more metal ions are taken up than correspond to the rest of the isotherm, which means that at the lowest concentrations all the constants a and b become larger.

Apart from reasons of their simple determination, copper and manganese had been chosen because they represent solutes which are, on this adsorbent, very difficult to separate. Their exchange affinities differ less than those of nickel and cobalt on alumina and they thus afford a particularly stringent test for both theory and practice.

Fig. 2A shows the measured elution curve of a manganese–copper separation in a column 1 m. long containing 60 g. of acid Zeo-karb H.I. In spite of the considerable length of column and the consequent increase of all disturbing factors, the theoretically vertical front boundaries were found to be exceedingly sharp—not only did the self-sharpening front boundary of pure manganese rise up within 1 c.c. of eluate, but even the practically non-self-sharpening front boundary of the copper against the frontal band of manganese is almost completely contained within 2 c.c. of eluate. It can therefore be assumed that equilibrium is almost complete at every point of the column. (For a detailed discussion on non-equilibrium phenomena at boundaries, see Part IV.)

Fig. 2B gives the elution curve calculated on the basis of the given constants (see legends of Fig. 2) by means of the equations deduced in Part I (*loc. cit.*) which are summarised at the beginning of this paper. In these calculations the pore space $a = 0{\cdot}7$ c.c./g. of adsorbent, which had been determined by direct measurement, has been taken into consideration.

The agreement between experiment and calculation is quite good except at the tail end of the chromatogram where the concentrations are very low and where, as mentioned before, the constants of the isotherm become larger. As a result, the tail is considerably longer than would be the case for a " pure " Langmuir isotherm and the concentration (c_{2_0}) at the front of the pure rear band of solute 2 is consequently reduced. Agreement is particularly good for the front part of the chromatogram, in particular for the threshold volume, and the sharp rise in the concentration of solute 1 at the inter-front (at $v = 36$ c.c.), which is to be expected for solutes of very similar adsorption affinity, is clearly shown.

The not inconsiderable disagreement in the details of the rear boundaries is of particular interest, because it shows the enormous sensitivity of the form of the rear boundary against minor variations in the form and shape of the isotherm.

If the isotherm is calculated from the rear boundaries of both the experimental and the calculated elution curve on Fig. 2, the two isotherms are practically indistinguishable between the concentrations of 0·02 to 0·09 milliequiv./c.c., as is seen from the following data :

	q_{Cu} (milli-equiv./g. of Zeo-karb).	
[Cu].	Calc. from exp. chromatogram.	Calc. for Langmuir isotherm.
0·093	0·176	0·175
0·065	0·130	0·1315
0·038	0·083	0·0835
0·019	0·046	0·044
0·006	0·017	0·014
0·002	0·007	0·005

The difference at the very lowest concentrations, which are practically inaccessible to ordinary equilibrium measurements, can thus with the greatest ease be recognised and calculated from the rear boundary of a chromatogram.

It is apparent therefore that, with the exception of threshold values, there is little hope of being able to calculate the shape of chromatograms if only the approximate forms of the isotherms are known. The value of the theory lies rather in the opposite direction in that it provides a convenient tool for the calculation of the isotherms, in particular of multiple isotherms from chromatographic data.

An example of a chromatogram where " development " has not been completed is shown in Fig. 3, Here the two front boundaries rise up steeply within about 3 c.c. of eluate. There follows the flat non-developed section, after which a rapid fall in the concentrations of both solutes takes place which, owing to small deviations in the isotherm, is again sharper than one would expect for the Langmuir type.

Fig. 4 shows the details of a few measured rear boundaries. Though relatively less important for the technical separation, these rear parts form a good test of the theory. Both c_{2_0} and the amount μ_2 separated at the rear are, according to the theory, dependent on the ratio c_1^0/c_2^0 of the initial concentrations, which in these three experiments have been varied over a wide ratio. The agreement between the calculated and the observed elution curves is as good as can be expected. Not only c_{2_0} and μ_2, but also the form of the rear band of pure solute 2 and the position of the point where solute 1 becomes zero, clearly show the trend demanded by theory.

DURHAM COLLEGES IN THE UNIVERSITY OF DURHAM. [*Received, November 20th*, 1946.]

241. *Theory of Chromatography. Part IV. The Influence of Incomplete Equilibrium on the Front Boundary of Chromatograms and on the Effectiveness of Separation.*

By E. Glueckauf and J. I. Coates.

It is shown that in the chromatographic column, under the usual working conditions, complete local equilibrium is not obtained. A theory is developed for the effect of incomplete equilibrium on chromatographic boundaries, and the form of observed boundaries agrees with those calculated. On decrease of grain size and flow velocity, equilibrium becomes more complete, and then some chromatographic separations can be effected with ease which are impossible by the usual methods; *e.g.*, the separation of nickel and cobalt ions on alumina.

(a) *Chromatographic Boundaries.*—The influence of incomplete local equilibrium is very similar to a diffusion effect and so shows itself most markedly at the boundaries of the chromatograms where high concentration gradients exist. Normal binary chromatograms when fully developed have, in the absence of disturbing effects, the form shown in Fig. 1 of the preceding paper. We may distinguish here two types of boundaries: (i) sloping rear boundaries such as *AB*, *CD*, and *C'D'*, and *L'Q*, and (ii) sharp front boundaries such as the threshold boundary *HG* or *PQ* and the inter-boundary *EF*, *E'F'* or *LK*, *L'K'* which is the front of solute 2. As has been shown by De Vault (*J. Amer. Chem. Soc.*, 1943, **65**, 532) the two front boundaries have normally (*i.e.*, for isotherms concave against the *c*-axis) self-sharpening properties. This means that, even if by some artificial means *HG* were made sloping, it would again become vertical during the process of development—at least theoretically. This self-sharpening tendency increases with the curvature of the isotherm and it is nil for linear isotherms (see De Vault, eqn. 7).

In the case of the threshold boundary *HG*, the self-sharpening effect is usually very considerable, as linear single-solute isotherms are rare. In the case of the inter-boundaries *EF* the corresponding function depends essentially on the "exchange" isotherm between the two solutes. If the two solutes are very different and easily separable, this boundary, too, usually shows considerable self-sharpening, but if the two solutes are very similar, the exchange isotherm is practically linear and then this effect is negligible. The inter-boundary is then referred to as a non-sharpening front boundary.

(b) *Attainment of Complete Equilibrium.*—In order to study the effect of non-equilibrium and diffusion phenomena, chromatographic elution curves were measured, using adsorbents of different grain size. The adsorbents were ground to a diameter as low as 0·01 mm. (as compared with the commercial grain sizes of about 0·08 mm.), and a uniform grain size was obtained by elutriation in air streams of varying velocity.

The flow rate of the solvent in the chromatographic column was varied from 0·001 cm./sec., which means 1 drop in 2 mins. for a tube of 1 cm. diameter, to the usual flow rates of 10—60 drops per min.

Systematic experiments showed that the quality and sharpness of non-sharpening inter-boundaries, *e.g.*, such as between copper and manganese ions on Zeo-karb H.I. or H.I.P., continuously increased with reduction of grain size and flow rate. There must be an optimum flow rate, as the latter can obviously not be infinitely decreased without introducing disturbances on account of diffusion. But this latter effect is so small compared with the non-equilibrium effect and other disturbances that even at the lowest flow rates used an improvement was still noticeable compared with faster flow rates.

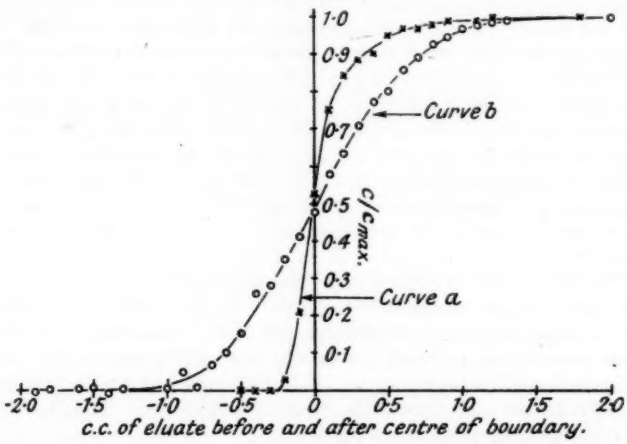
Under the conditions mentioned above ($d = 0{\cdot}01$ mm., $F = 0{\cdot}001$ cm./sec.), we were able to obtain, for a column of 1 m. length, non-sharpening inter-boundaries between 0·6 and 1 cm., and self-sharpening front boundaries extending on one occasion over only 0·10 cm., the former corresponding to 0·5—1%, the latter to 0·1% of the threshold volume.

That these conditions are not obtained with the usual practice can be seen from Fig. 10*a* of Weil-Malherbe (*J.*, 1943, 303), which contains about the best chromatographic experiments published. Here a non-sharpening front (benzpyrene on silica gel) extends over 25% of the threshold volume, and a strongly self-sharpening one (benzpyrene on alumina) over 12% of the threshold volume. A check on the form of non-sharpening front boundaries is therefore essential in all experimental work connected with the study of elution curves and, in particular, in such cases where elution curves are used for the calculation of adsorption equilibria (see Glueckauf, *Nature*, 1945, **156**, 748, and Part II).

Although it is apparent that non-equilibrium phenomena can easily occur in the case of exchange materials, it is not usually realised that the same, though perhaps to a lesser degree, also applies to the so-called " adsorbents " like alumina and calcium carbonate, as adsorption takes place not only on the surface, but also inside the grains. The reason for this is that most experimenters investigating the form of bands have worked with single solutes which usually have strongly self-sharpening fronts. These maintain a reasonable sharpness even if considerably disturbed by non-equilibrium phenomena. Consequently, observers are easily deceived by this appearance of moderately sharp fronts, which are usually taken as proof of the absence of non-equilibrium phenomena.

How far the process of wishful thinking can go is shown, *e.g.*, by Jacobs and Tompkins (*Trans. Faraday Soc.*, 1945, **41**, 401, Fig. 1, Curve A), who convinced themselves—with the help of the equilibrium curve applied to a diffuse non-equilibrium boundary—that, in spite of the very diffuse eluted front which they found, the front of the adsorbate in the column

FIG. 1.



Experimentally measured boundaries. (a) *Self-sharpening threshold boundary of* N-$CoCl_2$ *solution in column of acid Zeo-karb.* (× — × — ×) (*compare with curve calculated for* $bc^0 = 10$ *in Fig.* 4). (b) *Non-sharpening inter-boundary between frontal band of* $^{59}CoCl_2$ *and mixed band of* $^{59}CoCl_2$ *and* $^{60}CoCl_2$ *in same column of Zeo-karb* (○— ○—○) (*symmetrical* **S** *shape*).

must have been very sharp. By doing so, they overlooked the fact that a sharp front of adsorbate moving through the column must deliver the solute at the end in an equally sharp-fronted elution curve—simply by reason of the conservation of matter (for details see eqn. 5).

The non-equilibrium phenomena, however, become very obvious when fronts are concerned which have little or no self-sharpening properties, *e.g.*, the boundary of one solute against another of similar adsorption affinity. As it is just such a boundary which occurs at the point of separation of two similar solutes (boundary *EF* in Fig. 1 of Part III), these non-equilibrium effects greatly reduce the efficiency of the separation.

(c) *Form of the Disturbed Self-sharpening Front Boundary.*—No theory has so far been given for the theoretical form of a front boundary disturbed by non-equilibrium phenomena in the case of a non-linear isotherm. Weiss (*J.*, 1943, 301; eqns. 59—62 and Fig. 5) has produced a schematical representation for the case of a linear isotherm which, however, apart from the diffuseness, does not really represent the experimental facts (see our Fig. 1, curve *b*, showing that the measured elution curve of a front boundary for a strictly linear isotherm has a symmetrical sigmoid form. A similar conclusion has also been reached by Klotz, *Chem. Rev.*, 1946, **39**, 243). A satisfactory theory for the case of the linear isotherm has been produced by Dr. H. London which, however, has not yet been published.

In the case of a self-sharpening front boundary caused by a non-linear isotherm, the general differential equations become very complicated, but, after the front has travelled some distance, a final form is attained which can be represented by a simple equation. Here the effects of non-equilibrium and self-sharpening just balance each other. For simplicity the calculations are carried out for the " undeveloped " chromatogram where the front has the original concentration c^0.

In the case of non-equilibrium, the usual chromatographic equation of mass conservation (see Part II, eqn. 2), *viz.*,

$$[\Delta v/\Delta x]_c = \mathrm{d}f^*_{(c)}/\mathrm{d}c + \alpha \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

changes to

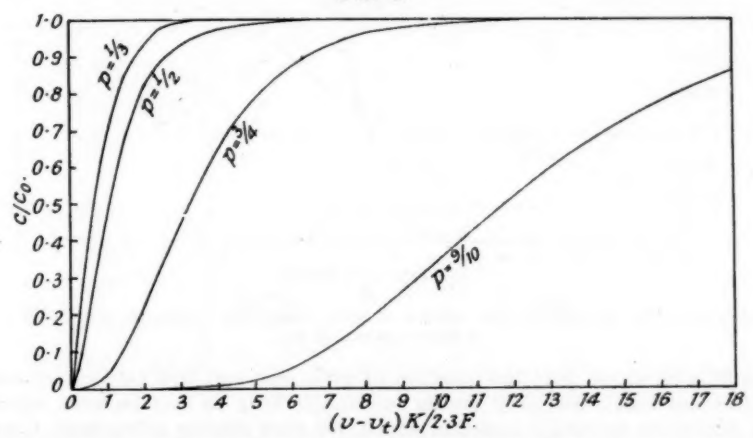
$$[\Delta v/\Delta x]_c = \mathrm{d}q^*/\mathrm{d}c + \alpha \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

where q^* is the amount actually adsorbed, the missing amount $(f^*_{(c)} - q^*)$ being due to dis-equilibrium. When at a given point (x) of the front boundary the concentration rises during the passage of the front through this point, q^* is, with good approximation, represented by the equation

$$\mathrm{d}q^*/\mathrm{d}t = K(f^*_{(c)} - q^*) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

which means that the rate of diffusion into the grains is essentially proportional to the amount still required to produce equilibrium. Here K is a diffusion factor (the inverse of the time in which a grain of adsorbent reaches 1/e of its equilibrium adsorption), and $K = D/(\eta d)^2$, where D is the diffusion constant of the solute in the solid material, d is the grain diameter, and $\eta(<1/2)$ depends on the geometry of the grains.

FIG. 2.



Self-sharpening front boundaries for solutes obeying Freundlich isotherms $q = ac^p$ *for different values of* p.

After competition between the self-sharpening and the non-equilibrium effects has resulted in a final form of the front boundary, the whole front boundary and thus also the point of concentration c move with the usual velocity of the sharp undeveloped front boundary

$$[\Delta v/\Delta x]_c = f^*_{(c^0)}/c^0 + \alpha \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

It follows from equations (2) and (4) that in this final state

$$\mathrm{d}q^*/\mathrm{d}c = f^*_{(c^0)}/c^0 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

This means that, no matter what the form of the equilibrium isotherm, q^* must always be a linear function of c. Eliminating q^* by means of (5) in (3) and replacing t by v/F (where F = flow velocity of solvent, in c.c./sec.), we get

$$\mathrm{d}c/\mathrm{d}v = (K/F)[f^*_{(c)} \cdot c^0/f^*_{(c^0)} - c] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

Equation (6) has a particularly simple form in the case of the Freundlich isotherm

$$f^*_{(c)} = A \cdot c^p \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

Integration of (6) then leads to the equation for the elution curve of a disturbed self-sharpening front (final state) :

$$v - v_t = \frac{-F}{K(1-p)} \cdot \log\,[1 - (c/c^0)^{(1-p)}] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

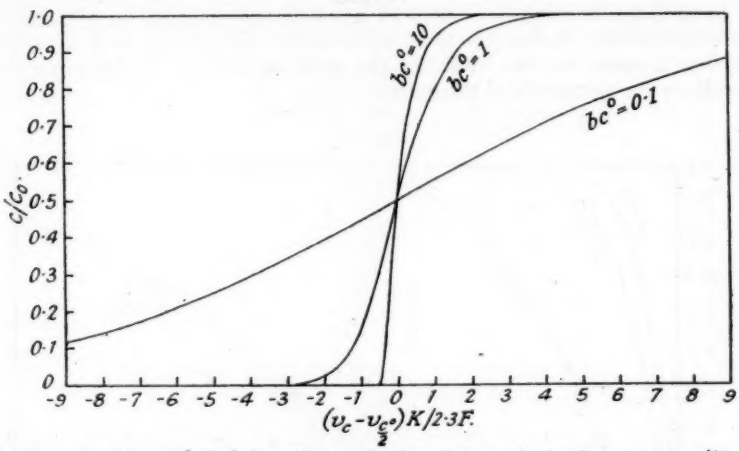
Similarly one obtains for the frontal distribution in the column

$$x_f - x = \frac{-F}{K(1-p)} \cdot \frac{c^0}{f_{(c^0)}} \cdot \log\,[1 - (q^*/q^0)^{(1-p)}] \quad . \quad . \quad . \quad . \quad . \quad . \quad (9)$$

where x_f is the most advanced point of the front boundary. Equation (8) requires that the length of the eluted front is independent of the concentration c^0, which is perfectly shown in Jacobs and Tompkins's Fig. 2 (*loc. cit.*, p. 402). Equation (8) also shows the effect of p on the slope and extension of the front boundary, which is demonstrated in the experiments of Weil-Malherbe (*loc. cit.*, Fig. 10*a*), though not quantitatively, since, with the short columns used, the final state is not attained for values of p near unity.

Fig. 2 gives the theoretical curves of eluted front boundaries in the stationary state for various values of p. It shows that for small values of the Freundlich exponent p (*e.g.*, $p = \frac{1}{3}$) the front rises sharply but reaches the maximum (c^0) only asymptotically. For comparatively large values of p it has a sigmoid form, which for $p = \sim 1$ reaches both the values $c = 0$ and $c = c^0$ asymptotically.

FIG. 3.



Self-sharpening front boundaries for solutes obeying Langmuir isotherm $q = ac/(1 + bc)$ *for different values of* bc^0.

Equation (8) also shows that the question of grain size and flow rate comes into play to a very marked extent only when very similar substances have to be separated, where the inter-boundary is due to an exchange isotherm which, for very similar substances, is almost linear ($1 - p = \sim 0$; thus $v - v_f = \sim \infty$). No final state is attained by the front boundary when $p = 1$ (linear isotherm), under which conditions there is no self-sharpening effect, and, consequently, the slope of such a front boundary continues to decrease indefinitely.

Very similar conditions arise in the case of the Langmuir isotherm

$$f^*_{(c)} = ac/(1 + bc) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (10)$$

Here integration of eqn. (6) leads to the equation for the elution curves :

$$v_c - v_{\frac{c^0}{2}} = -\frac{K}{F}\left[\frac{1}{bc^0} . \log (c^0 - c)/c + \log 2\,(c^0 - c)/c^0\right] \quad . \quad . \quad . \quad . \quad (11)$$

The form of the front boundary here depends on bc^0 which, according to the physical interpretation of the Langmuir isotherm, is the ratio of covered to free adsorbing surface. As can be seen from Fig. 3, the self-sharpening tendency increases with bc^0, *i.e.*, with increasing surface saturation. A comparison with Fig. 2 shows that there is a complete parallelism in the form of the front boundaries for the two isotherms, small values of p corresponding to large values of bc^0 and *vice versa*.

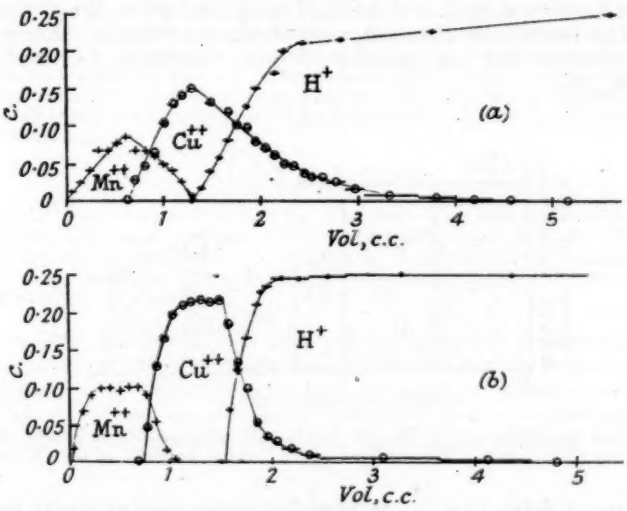
The diagrams of two accurately measured front boundaries are shown in Fig. 1. Curve *a* is the eluted front boundary of a 1N-[$CoCl_3$] band after passing 3*g* of acid permutite. The isotherm is approximately of the Langmuir type with a value of $b \simeq 3$—4 (thus $bc^0 = 3$—4). A comparison with the corresponding calculated curves in Fig. 3 shows a good agreement. Curve *b* shows an inter-boundary between a mixture of ^{59}Co and ^{60}Co against a front-band of pure ^{59}Co, where the rise in the concentration of ^{60}Co has been measured. As the exchange isotherm between the two isotopes is strictly linear, there is no self-sharpening to be expected, and the experiment shows, in agreement with the theory, a symmetrical S-form for this front boundary.

The elution curve of the boundary of the two isotopes was measured by means of the β activity of ^{60}Co ($\tau = 5{\cdot}5$ years) in single drops of eluate which were dried on filter-paper.

(d) *Effect of Non-equilibrium on Separation of Two Solutes.*—A typical example of the importance of such considerations is shown in the separation of copper and nickel on commercial alumina by Jacob and Tompkins (*loc. cit.*, p. 398, Fig. 3), using a linear flow velocity of 0·07 cm./sec. Even after the band has travelled several times the distance which they expect to be required for complete separation, the mixed part of the band still contains about 70% of the nickel and about 30% of the total copper.

We obtained very similar results with copper and manganese (the latter being used instead of nickel owing to its easy volumetric determination). Using a flow velocity of 0·027 cm./sec. and 0·25N-sulphuric acid for elution on 2·2 g. of commercial alumina, we obtained the elution curve of Fig. 4*a*, which shows the retention of a mixed band with 47% of the manganese and about 25% of the copper. (Figs. 4*a* and *b* were obtained by analysing single drops of eluate.)

FIG. 4.



Elution curves of mixture of $CuSO_4$ *and* $MnSO_4$ *chromatographed on 2·2 g. of* Al_2O_3. *Development with* 0·25N-H_2SO_4.

Abscissa : volume of eluate after appearance of solute in eluate.
Ordinate : concentration of solutes in eluate (milliequiv./c.c.).
(a) *Diameter of* $Al_2O_3 = 0{\cdot}08$ *mm.; flow velocity* $= 0{\cdot}027$ *cm./sec.*
(b) *Diameter of* $Al_2O_3 = 0{\cdot}01$ *mm.; flow velocity* $= 0{\cdot}0014$ *cm./sec.*

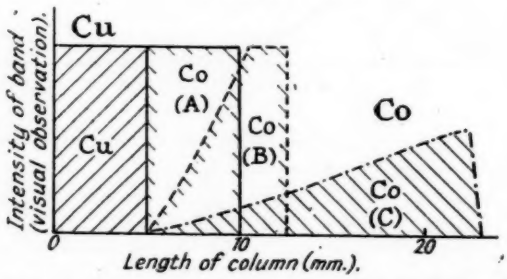
By reducing the grain size from 0·08 to 0·01 mm. diameter and the flow velocity to 0·0014 cm./sec., and otherwise using identical conditions, the effect of the diffusion and non-equilibrium phenomena was much reduced (see Fig. 4*b*). The mixed part of the band now contained only 20% of the manganese and 14% of the eluted copper, and in some experiments still less. (Actually, separation appeared to be much more complete in the column, and the small amount of mixing observed in the eluate seemed to be due to the mixing of 2 or 3 drops at the bottom of the tube.) Also, in other respects, the two experiments show marked differences. In the second experiment (Fig. 4*b*) all the front boundaries of the Mn^{++}, Cu^{++}, and H^+ are fairly steep, and the flat levels of the manganese and copper bands show clearly that these bands are not being "developed" by a diffuse rear boundary, a feature which is lost completely through non-equilibrium phenomena in Fig. 4*a*, and in the copper elution curves of Jacob and Tompkins (*loc. cit.*, p. 402, Fig. 2).

Although, under ordinary working conditions (commercial grain size and usual flow rate), some separation is still shown in cases where the differences in adsorption affinity and the self-sharpening tendencies of the inter-front are comparatively large, as is the case for Cu–Ni and Cu–Mn, it becomes impossible to separate solutes of very similar adsorption affinity, which consequently have fairly linear exchange isotherms, and whose inter-front is practically non-self-sharpening.

Such solutes as, *e.g.*, the group Ni, Co, Cd, Fe^{II}, are usually considered as non-separable (see Schwab and Jockers, *Z. angew. Chem.*, 1937, **50**, 646), but their inseparability is entirely due to the disturbing influence of diffusion and non-equilibrium phenomena which almost completely undo any chromatographic separation. No difficulty is experienced in effecting an almost complete separation—with adjoining bands, of course—between any two of these solutes if a smaller grain size and a lower rate of flow is employed. To give an example: 0·15 c.c. of 0·5N-$NiSO_4$ + 0·5N-$CoSO_4$ were developed with 0·25N-H_2SO_4. The original band, in a column of alumina of 8 mm. diameter, had a length of 4·5 mm. The band at first broadened on development with the more dilute acid and, by the time the just visible rear band of nickel had travelled 6 mm., separation was complete, the nickel occupying a position between 6 and 12 mm., and the cobalt that from 12 to 18 mm. Treatment with dimethylglyoxime and ammonia showed that, if there were any overlap between the nickel and the cobalt zone, it must have been less than 1 mm. A quantity of 0·3 g. of alumina thus proved to be sufficient to separate almost quantitatively 0·15 milliequiv. of the " inseparable " cobalt–nickel sulphate mixture.

It should also be mentioned that, as a result of using finer grain, the quality of packing was much improved. The boundaries obtained were absolutely straight. Fringes—only observable under the microscope—did not exceed 3—4 grain diameters, *i.e.*, 0·04 mm. on any of the boundaries of Fig. 4*b*.

FIG. 5.



Chromatogram of mixture of $CuSO_4$ *and* $CoSO_4$ *on* Al_2O_3. *Development with* $MnSO_4$ *solution.* Cu *band remains at the top of the column. Three stages in the " development " of the* Co *band are shown.*

(e) *Separation into Isolated Bands.*—As the slow separation of metal ions on fine-grain alumina proved so successful, an attempt was made to obtain a complete separation into isolated bands. With acid as developing agent, this is of course not possible, as hydrogen ions are the most strongly adsorbed ions and, consequently, the bands cannot be expected to separate (see Glueckauf, Part I, *Proc. Roy. Soc.*, 1946, *A*, **186**, 50, case 4). If a complete separation, *e.g.*, of copper and cobalt bands is required, development must be attempted with a less adsorbed solute, such as Mg^{++} or Mn^{++} solutions.

Fig. 5 shows the approximate distributions of the separated bands observed during a chromatographic separation of 0·15 c.c. of 0·5N-$CuSO_4$ + 0·5N-$CoSO_4$, developed with 1, 1·5, and 4·5 c.c. of 0·5N-$MnSO_4$ solution. Already after 1 c.c. of developing solvent had been added, the separation of copper and cobalt seemed almost complete, resulting in adjoining bands of about equal width. Further development hardly altered the position of the copper band. The front of the cobalt band continued to move down the column, but the tail end, though greatly decreasing in concentration, never moved away from the front of the copper band, a typical sign that cobalt ions follow a Freundlich isotherm even in the presence of 0·5N-Mn^{++}. (During the development it looked as if the bands were actually completely apart, but subsequent treatment with ammonium sulphide showed that the cobalt band reached right back to the copper front.)

Thus, if separation into two entirely separated bands were required, it would in this case be necessary either to develop with a solute of intermediate adsorption affinity (*e.g.*, zinc), or to add such a solute to the mixture and develop with acid.

Somewhat similar is the separation of nickel and cobalt with 0·5N-$MnSO_4$ solution as developing agent. Here both bands attained a triangular shape of approximately equal length, the nickel band beginning at the top of the column, and the cobalt band at the fairly sharp front of the nickel band. (The cobalt band was here not actually a triangle, but began

with a definite concentration, as must be expected for Freundlich isotherms. This is shown in detail in Figs. 4, 5, and 6 of Part V.)

Our thanks are due to Dr. H. London, University of Birmingham, who first drew our attention to the great importance of non-equilibrium phenomena for the separation of solutes of very similar adsorption affinity.

DURHAM COLLEGES IN THE UNIVERSITY OF DURHAM. [*Received, November 26th*, 1946.]

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242. *Theory of Chromatography. Part V. Separation of Two Solutes Following a Freundlich Isotherm.*

By E. GLUECKAUF.

An attempt is made to predict the behaviour during chromatographic separation of solutes following individually a Freundlich isotherm $ac = q^n$. A method is shown for the graphical solution of the fundamental chromatographic equation $dq_1/dc_1 = dq_2/dc_2$, which makes it possible to calculate the distribution of solutes in binary chromatograms for any type of isotherm. It is shown that in the case of Freundlich isotherms two essentially different types of chromatogram must be expected (see Figs. 4 and 6). In order to obtain complete separability into two adjoining bands the condition must be fulfilled that the molar phase ratio at the point of separation of the bands

$$\left[\frac{q_2}{c_2}\cdot\frac{c_1}{q_1}\right]_0 > n_2$$

If the leading solute has the lower value of n, *i.e.*, if $n_1 < n_2$, this can always be achieved by working at low enough concentrations. If this condition is not fulfilled, solute 2 cannot be obtained pure, but can only be enriched. Pure solute 1 can always be obtained, though in the latter case not quantitatively. Chromatographic separation is the easier the smaller the ratio n_1/n_2 of the Freundlich exponent.

(a) *An Isotherm for Multiple Solutes.*—The case of the Langmuir isotherm has been dealt with in considerable detail in an earlier publication. In deducing what happens in the case of two substances each following a Freundlich isotherm, the difficulty arises that no isotherm of the Freundlich type has so far been suggested for multiple solutes. Nevertheless, we may assume that, just as the simple Freundlich isotherm $q = (ac)^n$ can be replaced by a sum of Langmuir equations

$$q = \sum_1^\nu \frac{a_\nu c}{1 + b_\nu c} \quad \ldots\ldots\ldots\ldots \quad (1)$$

as has been suggested by Hinshelwood (" Kinetics of Chemical Change in Gaseous Systems ", 2nd edition, p. 195), the multiple Freundlich isotherm, if it existed, might be synthesised as

$$q_1 = \sum_1^\nu \frac{a_{1\nu}c_1}{1 + b_{1\nu}c_1 + b_{2\nu}c_2} \quad \ldots\ldots\ldots\ldots \quad (2)$$

An isotherm of this type, which still has a finite slope (dq/dc) at $c_1 = 0$ would show little difference in principle from the chromatographic behaviour of a " pure " Langmuir isotherm, and such differences would be confined mainly to a smaller rate of separation at the rear end (see, *e.g.*, Part III, Fig. 2).

Another possibility is to write the Freundlich equation in the form

$$ac = q(q)^{n-1} \quad \ldots\ldots\ldots\ldots \quad (3)$$

and compare it with the Langmuir equation in the form

$$ac = q(1 - \beta q)^{-1} \quad \ldots\ldots\ldots\ldots \quad (4)$$

where $\beta = b/a$ represents the amount of adsorbent occupied at saturation by 1 mol. of adsorbate. If the mechanism of adsorption is similar, we may reasonably assume that in both cases the concentration of the solute is in the first instance proportional to the concentration in the adsorbed state (q), modified by a factor which is dependent on the amount of free adsorbing space still available, which is a function of the amount absorbed. In the case of the multiple Langmuir isotherm this modifying function is

$$\left[1 - \beta_1\left(q_1 + \frac{\beta_2}{\beta_1}q_2\right)\right]^{-1}$$

We may assume that a similar additivity would exist for the occupied surface areas in the case of the modifying function of a multiple Freundlich isotherm, which would then have the form, analogous to eqn. (3):

$$\left.\begin{aligned} a_1c_1 &= q_1\left(q_1+\frac{\beta_2}{\beta_1}q_2\right)^{n_1-1} \\ a_2c_2 &= q_2\left(\frac{\beta_1}{\beta_2}q_1+q_2\right)^{n_2-1} \end{aligned}\right\} \quad \ldots\ldots\ldots \quad (5a, b)$$

Equation (*5a, b*), which, like the Freundlich equation, can only be considered as empirical, should make it possible to predict the conditions of mixed adsorption when the single-solute isotherms are known, at least if the surface requirements β can be considered identical.

Actually it is possible to make physical assumptions which link the Freundlich isotherm with the theoretically deduced Langmuir equation (though it cannot be discussed here how far these assumptions are justified). We may assume that every part of the surface can become an actively adsorbing spot, if raised temporarily to a higher energy level P which in this case corresponds to a state of unsaturation. The higher this degree of unsaturation, the larger must be the activation energy P, but the greater will be the amount of desorption energy Q which an adsorbed solute requires for its removal from this activated spot. The simplest assumption would be that P and Q form, at a given temperature, a definite ratio $P/Q = m$, where $m < 1$, so that activation + adsorption results in an exothermic process.

A Maxwell–Boltzmann distribution being assumed for the P levels, the proportion of active surface ΔS_Q adsorbing with an adsorption energy between Q and $Q + \Delta Q$ is

$$\frac{\Delta S_Q}{\Delta Q} = \frac{m}{RT}\cdot e^{-mQ/RT} \quad \ldots\ldots\ldots \quad (a1)$$

There is no reason why in normal cases a group of active spots of uniform properties should not adsorb according to the Langmuir isotherm:

$$\Delta q_Q = \frac{\Delta S_Q}{\beta}\cdot\frac{Kc\,e^{Q/RT}}{(1+Kc\,e^{Q/RT})} = \frac{\Delta S_Q}{\beta}\cdot\frac{b_Qc}{1+b_Qc} \quad \ldots\ldots\ldots \quad (a2)$$

Replacement of ΔS_Q in (*a2*) by means of (*a1*) and elimination of Q by b_Q leads to the equation

$$\Delta q_Q = \frac{mK^mc}{\beta\cdot b_Q^m(1+b_Qc)}\cdot\Delta b_Q \quad \ldots\ldots\ldots \quad (a3)$$

and integrating over all values of Q, *i.e.*, for all adsorption factors b from 0 to ∞, we have

$$q = \frac{mK^mc}{\beta}\int_0^\infty \frac{db}{b^m(1+bc)} \quad \ldots\ldots\ldots \quad (a4)$$

which for $0 < m < 1$ results in

$$q = \frac{m\pi K^m}{\beta\sin m\pi}\cdot c^m = Ac^m \quad \ldots\ldots\ldots \quad (a5)$$

This is the well-known form of the Freundlich isotherm.

The same considerations can be applied to the case of two solutes. This leads eventually to

$$q_1 = \frac{m_1K_1^{m_1}c_1}{\beta_1}\int_0^\infty \frac{db_1}{b_1^{m_1}\left[1+b_1c_1+\left(\frac{b_1}{K_1}\right)^{m_2/m_1}K_2c_2\right]} \quad \ldots\ldots \quad (a6)$$

which integral appears to be soluble only for the case $m_1 = m_2$. In this case, integration leads to equations for q_1 and q_2 which are almost identical with the equations *5c, d*. This gives some theoretical support for the multiple adsorption isotherms *5a, b*, though only in the case $n_1 = n_2$.

Unfortunately, very few experimental data on mixed adsorption are available to test the usefulness of equation (*5a, b*), one of the best examples being the adsorption of oxalic (1) and succinic (2) acids on charcoal (probably by Masius; see Freundlich, "Colloid and Capillary Chemistry," Methuen, Fig. 39, p. 200). The Freundlich isotherms of the single solutes obtained from the experimental data are $40c_1 = (q_1)^{2.1}$ and $216c_2 = (q_2)^{2.6}$, where c is measured in mol./l. and q in millimol. per g. of charcoal, from which would follow in accordance with eqn. (*5a, b*), the multiple isotherms

$$40c_1 = q_1\left(q_1+\frac{\beta_2}{\beta_1}q_2\right)^{1.1} \quad \ldots\ldots\ldots \quad (5a')$$

$$216c_2 = q_2\left(\frac{\beta_1}{\beta_2}q_1+q_2\right)^{2.6} \quad \ldots\ldots\ldots \quad (5b')$$

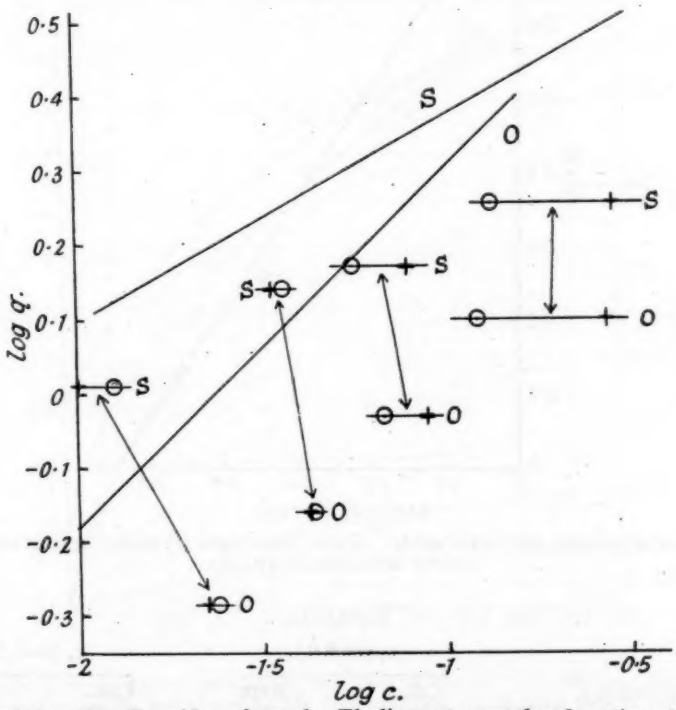
Fig. 1 shows the straight lines of the single-solute isotherms of succinic acid (*S*) and oxalic acid (*O*), as well as a number of points giving the measured adsorption equilibria for approximately

equimolar solutions of the mixed solutes, the points of coexisting concentrations being tied by arrows. From the values of q_1 and q_2 of these points the "theoretical" values of c_1 and c_2 have been calculated by means of eqns. (5*a*′) and (5*b*′), and the resulting points are shown in Fig. 1 as circles: β_2/β_1 has been chosen as 1·2 which slightly improves the agreement as compared with the assumption of equal surface requirements. Though the deviations of the calculated values of c_1 and c_2 from the observed values are not negligible, it is apparent that the equations (5*a*′) and (5*b*′), the constants of which are taken from the single-solute isotherm, express the conditions of mixed adsorption with reasonable approximation.

Much better is the agreement with the experimental values if we consider the effect of the total adsorbate on the molar phase ratio ξ obtained from eqns. (5*a*) and (5*b*):

$$\xi = \frac{c_1}{c_2}\Big/\frac{q_1}{q_2} = \frac{a_2}{a_1}\left(\frac{\beta_2}{\beta_1}\right)^{n_1-1}\cdot\left(\frac{\beta_1}{\beta_2}q_1 + q_2\right)^{n_1-n_2} \quad \ldots\ldots\ldots \quad (6)$$

FIG. 1.



Adsorption of succinic and oxalic acid on charcoal. The lines represent the adsorption of the single solutes; the points show the data of mixed adsorption of the two acids, coexisting concentrations being tied by arrows. (+) *observed data,* ⊙ *calculated from single solute isotherms by eqn.* (5*a*′, *b*′).

(see Fig. 2). Here the points correspond to the experimental values of c_1, c_2, q_1, q_2, and the line is obtained from eqn. (6) with $\beta_2/\beta_1 = 1{\cdot}2$, and all the other constants are taken from the single-solute isotherms. ξ is the separation factor and its importance for the chromatographic separation is similar to that of the molar phase ratio of the gaseous and the liquid phase for fractional distillation. The agreement is so much better here because any effects of mutual attraction or repulsion between the different adsorbed solutes, *e.g.*, due to the heat of mixing in the surface, which are not considered in eqn. (5*a*, *b*), are greatly reduced in ξ. This, too, has its parallel in the vapour pressures of binary liquids, where the agreement between theory and experiment is always better for the molar phase ratio than for the concentration–pressure curves.

Very similar conditions exist in the case of the binary adsorption of acetone (i) and acetic acid (ii) on charcoal. The single-solute isotherms are here (see experiments by Michaelis and Rona, *Biochem. Z.*, 1909, **15**, 204—207)

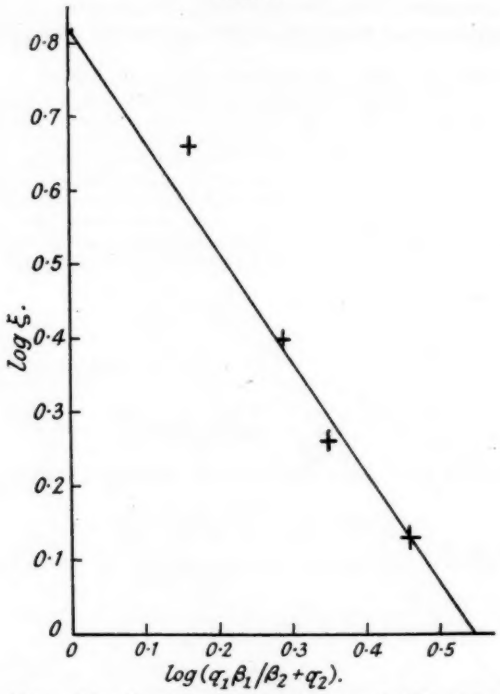
$$25c_1 = q_1^{2\cdot0} \text{ and } 41{\cdot}5c_2 = q_2^{3\cdot0}$$

so that one might expect the multiple isotherms

$$25c_1 = q_1(q_1 + \varepsilon q_2) \text{ and } 41{\cdot}5c_2 = q_2\left(\frac{q_1}{\varepsilon} + q_2\right)^2$$

At high concentrations of acetone, deviations due to the heat of mixing in the surface are again very marked, but at lower concentrations of acetone agreement is quite good (see Table I, where the concentrations in the solvent have been calculated for given quantities of adsorbate, using a value of $\varepsilon = 0{\cdot}65$), and Table II, where the amount of acetic acid required to produce a given distribution of

FIG. 2.



Mixed adsorption of succinic and oxalic acids. Molar phase ratio (ξ) plotted against mixed adsorption density according to eqn. (6).

TABLE I.

q_1 (milli-mol./g.).	q_2	c_1 (mol./l.). Calc.	c_1 (mol./l.). Exp.	c_2 (mol./l.). Calc.	c_2 (mol./l.). Exp.
0·25	0·25	0·0041	0·0016	0·0024	0·0010
0·57	1·30	0·032	0·029	0·148	0·144
0·42	1·90	0·028	0·031	0·296	0·302
0·51	2·04	0·037	0·030	0·39	0·30
0·37	2·60	0·030	0·033	0·625	0·628

TABLE II.

Total acetone used (milli-mol.).	q_1 (milli-mol./g.).	c_1 (mol./l.).	Acetic acid added (milli-mol.). Calc.	Exper.
0·209	0·043	0·0033	33·4	34·2
,,	0·055	0·0031	13·9	17·1
,,	0·061	0·0030	10·1	8·6
,,	0·129	0·0016	0·4	0

solute 1 between 50 c.c. of water and 1 g. of charcoal has been calculated from the adsorption data of solute 1.

These considerations should make it clear that substances separately obeying a Freundlich isotherm do not necessarily follow the binary isotherm (5*a*, *b*), but that this equation represents

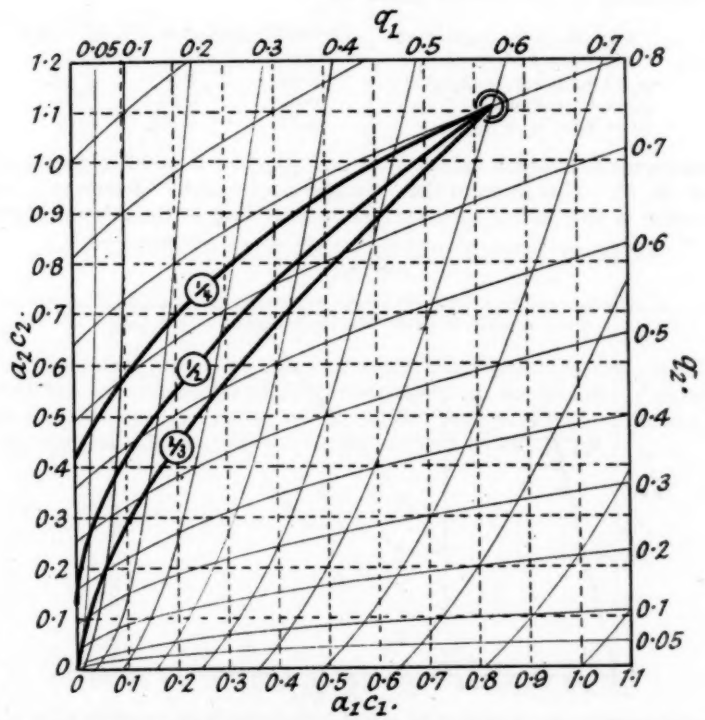
a function which contains many, though not necessarily all, the essential features, which may be expected from a multiple adsorption isotherm of such solutes. In particular, it contains the typical feature of the Freundlich isotherm of infinite slope at zero concentration.

For $n_1 = n_2$, $\beta_1 = \beta_2$. Eqn. (5*a*, *b*) can also be written in the form

$$\left.\begin{aligned} q_1 &= \frac{a_1 c_1}{(a_1 c_1 + a_2 c_2)^{1-1/n}} \\ q_2 &= \frac{a_2 c_2}{(a_1 c_1 + a_2 c_2)^{1-1/n}} \end{aligned}\right\} \quad \ldots\ldots\ldots \quad (5\,c, d)$$

which shows at the same time the formal resemblance to and also the essential difference from the multiple Langmuir isotherms.

FIG. 3.



Contour lines of the q_1–c_1–c_2 *and of the* q_2–c_1–c_2 *surfaces, as required for obtaining the curve of coexistent values of* c_1 *and* c_2 *in the mixed part of the chromatogram for a given case of initial concentrations* c_1^0, c_2^0 (O). *The three lines refer to three different values of* a_1/a_2 ($= \frac{1}{4}$, $\frac{1}{2}$, *and* $\frac{1}{3}$).

(b) *Chromatographic Separation in the Case* $n_1 = n_2$.—In order to apply chromatographic equations to either eqn. (2) or (5), it is necessary to solve the fundamental differential equations governing the chromatographic process $dq_1/dc_1 = dq_2/dc_2$. As has been pointed out in Part I (*Proc. Roy. Soc.*, 1946, *A*, **186**, 54), a general solution is so far only possible in the case of the " pure " Langmuir isotherm. We can, however, solve this equation by graphical evaluation and thus obtain the relationships between coexistent values in the chromatogram of c_1 and c_2 or q_1 and q_2 in any numerical case.

For this purpose lines of equal q_1 and of equal q_2 are plotted on a system with the co-ordinates a_1c_1 and a_2c_2 (or c_1 and c_2) (see Fig. 3). These represent the contour lines of the three-dimensional q_1–a_1c_1–a_2c_2 and q_2–a_1c_1–a_2c_2 diagrams. We may then start with a point [representing the conditions of the original solution (c_1^0, c_2^0) to be chromatographed] and, by a method of trial and error, find a neighbouring point which obeys the condition $\Delta q_1/\Delta c_1 = \Delta q_2/\Delta c_2$. Thence we proceed from point to point until one of the concentrations becomes zero. The resulting curve (thickly marked in Fig. 3) then represents the relationships between coexistent values in the mixed chromatogram of q_1 and q_2, c_1 and c_2.

In order to make a wider use of this diagram the evaluation has been made for three different values of a_1/a_2 ($= \frac{1}{4}, \frac{1}{2}, \frac{3}{4}$) which thus represent three different isotherms of the same type. The contour lines of Fig. 3 have been calculated for eqn. (5*a*, *b*) with $n_1 = n_2 = 2$ and $\beta_1/\beta_2 = 1$. In this case the position of the " coexistence line " depends on the ratio a_1/a_2 only, so no individual values need be assigned to these constants.

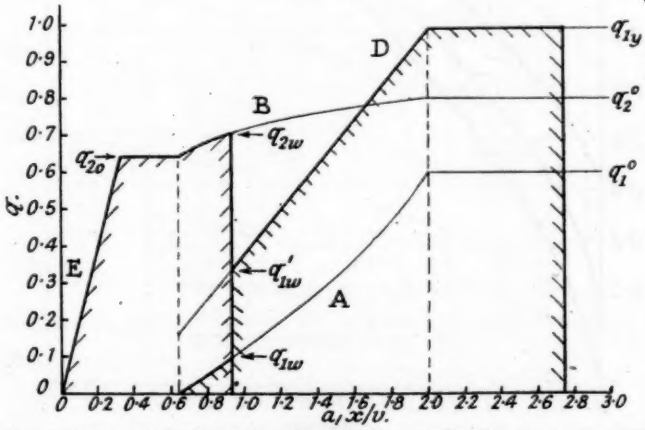
The starting concentrations of the adsorbate q_1^0 and q_2^0 have been chosen at random ($q_1^0 = 0{\cdot}6$, $q_2^0 = 0{\cdot}8$) and consequently $c_1^0 = 0{\cdot}84/a_1$, $c_2^0 = 0{\cdot}12/a_2$.

Each case of a_1/a_2 results in a function of coexistent values of c_1 and c_2 (and of q_1 and q_2, respectively) and these functions differ greatly in their characteristics. It can be shown that different starting points c_1^0, c_2^0, q_1^0, q_2^0 do not affect these characteristics, but that these depend on the ratio a_1/a_2 only. We always get types of function for coexistent values which can be represented with good approximation by the empirical equations (6*a*), (6*b*) and (6*c*), the value of the constants depending on the starting point.

a_1/a_2.	Equations for coexistent values of q_1, q_2.	Constants for $q_1^0 = 0{\cdot}6$, $q_2^0 = 0{\cdot}8$. k_1.	k_2.	k_3.	
$\frac{1}{4}$	$q_2 = k_1 + k_2 q_1 + k_3 q_1^2$	0·64	0·5	0·5	(6*a*)
$\frac{1}{2}$	$q_2 = k_1 + k_2\sqrt{q_1}$	0·37	0·55	—	(6*b*)
$\frac{3}{4}$	$q_2 = k_1^3\sqrt{q_1} + k_2 q_1$	0·77	0·25	—	(6*c*)

These relationships for coexistent values of q_1 and q_2 make it possible to substitute q_2 in the mixed isotherm (5*a*, *b*). This leads to the " pseudo-single-solute " isotherm $q_1 = F_{(c_1)}$ required for the construction of the binary chromatograms according to the general equations given in Part III.

FIG. 4.



Boundary lines of chromatograms calculated for mixed isotherm with the constants $n_1 = n_2 = 2$ *and mixed* $a_1/a_2 = \frac{1}{4}$. *Note similarity with the case of the Langmuir isotherm. Complete separation is attainable.*

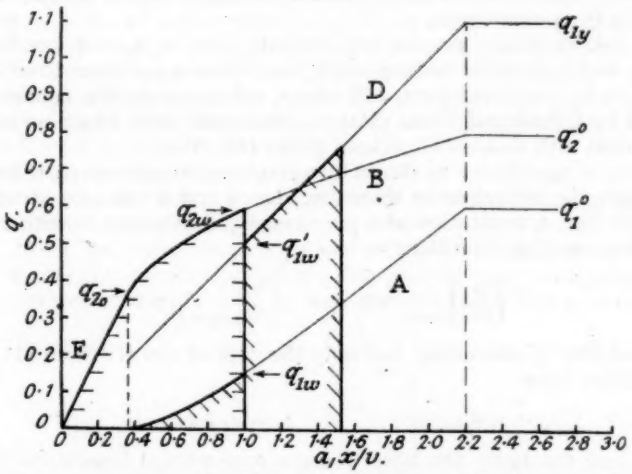
Figs. 4, 5, and 6 show the calculated loci of the chromatographic boundaries for the three cases considered ($a_1/a_2 = \frac{1}{4}, \frac{1}{2}, \frac{3}{4}$). Curves *A* and *B* represent the loci of the rear boundary of the mixed band for solute I and II respectively; curve *D* shows the rear slope of the pure frontal band of solute I, and curve *E* gives the diffuse rear boundary of the pure rear band of solute II. All the curves show the values of q_1 or q_2 plotted against the parameter a_1x/v as abscissa.

From these curves the actual form of the chromatograms can be obtained by fixing numerical values for the quantities of solutes (m_1, m_2) and for the volume v of solvent used. This defines the position x of the front boundaries of the mixed band and of the pure band of solute I. To make things clearer, these boundaries (for given cases of m and v) have been cross hatched; with these boundaries the abscissa represents the length of column (x) in an arbitrary unit.

We then see from Fig. 4 that, for solutes with values of $a_1/a_2 < \frac{1}{2}$, the general arrangement of the binary chromatogram shows little difference from that arising from a Langmuir isotherm (see Part I or Part III, Figs. 1*a–e*, Fig. 1*A*, *B*). The principal differences are that (*a*) the rear band does not separate from the top of the column, a known feature for Freundlich isotherms (see Weiss, *loc. cit.*, Fig. 4), and consequently is only very incompletely eluted, and (*b*) the

frontal band of solute 1 never completely separates from the rear band of solute 2, even after the mixed band has disappeared, because on account of the infinite value of dq/dc at $c_1 = 0$, the tail of the frontal band moves infinitely slowly and thus would always be overtaken by any other substance with $c > 0$ (see Fig. 5 of Part IV). The complete separation into two distinct bands

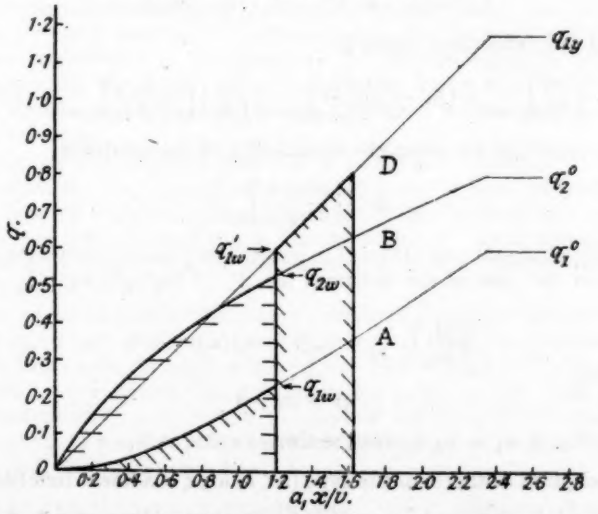
FIG. 5.



Boundary lines of chromatograms calculated for mixed isotherm with the constants $n_1 = n_2 = 2$ *and* $a_1/a_2 = \frac{1}{2}$. *Intermediate case between Figs. 4 and 6.*

of two solutes can therefore always be taken as a sign that the strict Freundlich isotherm does not apply to the faster-moving solute at very low concentrations, but that a pseudo-Freundlich isotherm of the type of eqn. (1) applies, which, as has been shown by a similar diagrammatic investigation, always permits separation into two distinct bands.

FIG. 6.



Boundary lines of chromatograms calculated for mixed isotherm with the constants $n_1 = n_2 = 2$ *and* $a_1/a_2 = \frac{1}{3}$. *Note that no pure solute II is separable; consequently no complete separation is attainable.*

This conclusion agrees with the experimental findings by Schwab and Jockers (*Z. angew. Chem.*, 1937, **50**, 646) that no white zones between coloured bands can be obtained when mixed inorganic solutes are chromatographed on alumina, where isotherms with Freundlich characteristics obtain.

The difference of the chromatograms from those of Langmuir isotherms becomes marked for small separability of the two solutes ($1 > q_1/q_2 > 0{\cdot}5$) (see Fig. 6). Here the flat portion at the front of the pure tail band of solute II and the discontinuity at this point disappear. On the other hand, there is no longer a point of complete separation, as the curve representing q_1 now runs right back to the top of the chromatographic column ($x = 0$). In this case, solute II cannot even partially be obtained in the pure state, though a certain amount of solute I can be obtained pure at the front boundary.

Between these two extremes lies the intermediate case, $a_1/a_2 = \frac{1}{2}$ (see Fig. 5). Here we have the very rare, and in practice never realised case where a pure rear band can form without a discontinuity at its forward boundary, and where, consequently, the equations (in particular 6 and 7) suggested by Offord and Weiss (*Nature*, **1945**, **155**, 725), which do not normally hold good, become identical with those of Glueckauf (*ibid.*, **156**, 205).

(c) *The Case of* $n_1 \neq n_2$.—It can be shown by a graphical integration (as in Fig. 3) that the two types of chromatographic behaviour as shown in Figs. 4 and 6 will also occur if $n_1 \neq n_2$. As in the case shown in Fig. 4, separation of a pure rear band of solute 2 (with a discontinuity at x_0) is confined to the essential conditions

$$\left[\frac{dc_1}{dc_2}\right]_{c_1=0} > 0 \quad \text{and} \quad \left[\frac{dq_1}{dq_2}\right]_{q_1=0} > 0 \qquad \ldots\ldots\ldots \quad (7)$$

This gives the possibility of discussing, not only the case of the isotherm (5*a*, *b*), but also the general isotherm of the type

$$c_1 = q_1\,\phi(q_1, q_2) \qquad\qquad c_2 = q_2\,\psi(a_1q_1, a_2q_2) \qquad \ldots\ldots\ldots \quad (8a, b)$$

where ϕ and ψ are any functions, the latter being a symmetrical function with respect to $\alpha_1 q_1$ and $\alpha_2 q_2$. Then

$$\left[\frac{dc_1}{dq_1}\right]_{q_1=0} = \phi(0,q_2) \qquad \ldots\ldots\ldots\ldots\ldots \quad (9)$$

$$\left[\frac{dc_2}{dq_2}\right]_{q_1=0} = \psi(0,q_2) + q_{2o}\left[\frac{d\psi}{dq_2}\right]_{q_1=0} \qquad \ldots\ldots\ldots \quad (10)$$

Equating (9) and (10) results in

$$\left[\frac{c_1}{q_1}\cdot\frac{q_2}{c_2}\right]_{q_1=0} = \xi_o = 1 + \frac{q_{2o}^2}{c_{2o}}\left[\frac{d\psi}{dq_2}\right]_{q_1=} \qquad \ldots\ldots\ldots \quad (11)$$

which, after partial differentiation, leads to

$$\left[\frac{dq_1}{dq_2}\right]_{q_1=0} = \left(\xi_o - \left[\frac{\partial \log c_2}{\partial \log q_2}\right]_{q_1=0}\right) \Big/ \frac{a_1}{a_1}\left(\left[\frac{\partial \log c_2}{\partial \log q_2}\right]_{q_1=0} - 1\right) \qquad \ldots\ldots \quad (12)$$

As $dq_1/dq_2 > 0$, the condition for complete separability of the solutes is

$$\xi_o > \left[\frac{\partial \log c_2}{\partial \log q_2}\right]_{q_1=0} \qquad \ldots\ldots\ldots\ldots \quad (13)$$

A useful application of (12) and (13) will in general be prevented by lack of knowledge of the value of q_{2o}. But in the case of the isotherm (5*a*, *b*), $[\partial \log c_2/\partial \log q_2]_{q_1=0}$ is independent of q_{2o} and results in

$$\left[\frac{dq_1}{dq_2}\right]_{q_1=0} = a_2(\xi_o - n_2)/a_1(n_2 - 1) \qquad \ldots\ldots\ldots \quad (12a)$$

and in the condition:

$$\xi_o > n_2 > 1 \qquad \ldots\ldots\ldots\ldots \quad (13a)$$

If, as in the case of Fig. 3, $n_1 = n_2$, ξ_o has the simple value a_2/a_1.

For a mixed adsorption isotherm of the type (5*a*, *b*) $\log \xi$ is a linear function of $\log\left(\frac{\beta_1}{\beta_2}q_1 + q_2\right)$, and we can have two different cases, according to whether n_1 (less adsorbed solute) is smaller or larger than n_2 (rear solute). In the first case when $n_1 < n_2$ (or more generally, when ξ increases with decreasing concentration) the condition $\xi_o > n_2$ is always fulfilled, as development can be continued until ξ is large enough (see Fig. 7*a*). The separation will be the more efficient the smaller $(q_1^0 + q_2^0)$, as this results in larger values of ξ^0 and ξ_o. This case behaves thus quite differently from that of the Langmuir isotherm, where separation is accelerated by working at high adsorption densities.

For the second case, when $n_1 > n_2$ (or more generally, when ξ decreases with diminishing concentration) (see Fig. 7*b*), it is apparent that the separation, which increases with ξ, improves with increasing concentrations of the solutes. If, however, they are not high enough to result in a value of $\xi_0 > n_2$ $\left(\text{or more generally } \xi_0 > \left[\frac{\partial \log c_2}{\partial \log q_2}\right]_{q_1=0}\right)$, which is essential for a clean separation of the solutes, the lowering of the concentrations in the course of the development will result in values of $\xi < 1$, at first for the rear, and eventually also for the front of the band. Thus, in the beginning, solute 1 will separate both in the front and in the rear with enrichment of solute 2 in the middle section of the band. Then, as the concentrations fall in the course of development, separation of solute 1 at the front will come to an end ($\xi_w = 1$) and will even be reversed ($\xi_w < 1$), whereby solute 2 again enters into the pure frontal band of solute 1 and eventually forms a frontal band of pure solute 2.

In this case, it is obviously much more economical to work from the start at such low concentrations that ξ^0 becomes < 1. This means that the solutes change their subscript and order in the chromatogram, reverting thereby to the case shown in Fig. 7*a*. It follows from this that chromatography at low enough concentrations will always lead to some kind of separation or enrichment in the case of Freundlich isotherms, though, if $n_1 > n_2$, chromatographic separation at high concentrations may in some cases ($\xi^0 \gg n_2$) result in a faster and more efficient separation,

FIG. 7 *a*.

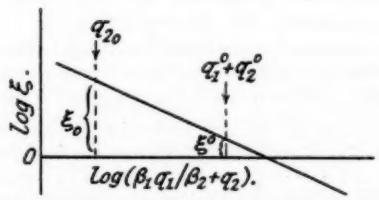
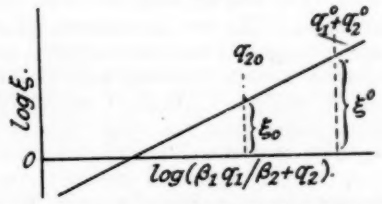


FIG. 7 *b*.



The separation factor ξ as function of the adsorption density. (a) $n_1 < n_2$: *separation improves with the use of lower concentrations.* (b) $n_1 > n_2$: *separation improves with increasing concentration of the solutes.*

particularly, when $c_1^0 \ll c_2^0$, which would result in a relatively large value of c_{20} and hence also of ξ_0 (of same order of magnitude as c_2^0 and ξ^0 respectively; this follows strictly for the Langmuir isotherm, and can be shown to be true for other isotherms by the graphical method).

The first of these conclusions is confirmed by the chromatographic practice, where low concentrations are generally favoured. The second case, where high concentrations improve the separation, and which has apparently so far not been looked for, will be investigated experimentally in due course.

It is also apparent from Fig. 7*a* and *b* that, if ξ^0 is identical for two pairs of solutes, where one has $n_1 < n_2$, and the other $n_1 > n_2$. separation will be far easier in the first case where the leading solute has the lower value of n, since during the process of development the value of ξ increases, while the converse is true if the leading solute has the higher n. More generally, it can be said that pairs of solutes with equal ξ can be separated the more easily the smaller the value of n_1/n_2.

These conclusions might be elaborated more quantitatively, if the proposed binary isotherm (5*a*, *b*) were more than a rough working model which, apart from the displacement effect, does not consider mutual influences on each other of the two solutes. The present state of our knowledge concerning binary adsorption isotherms, however, is such that much preliminary work must be directed towards establishing the mutual influence of adsorbed solutes on each other and the mathematical form of mixed isotherms, before further theoretical guidance can be given to the practical chromatographer.

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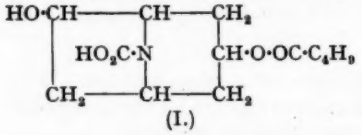
243. *The Minor Alkaloids of* Duboisia myoporoides. *Part IV. Valeroidine.*

By WILLIAM MITCHELL and E. M. TRAUTNER.

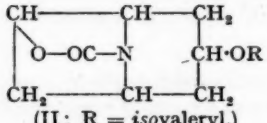
A final structure for valeroidine (*J.*, 1937, 1821; 1940, 1155) is proposed. The product of oxidation with permanganate in acetone is suggested to be an inner urethane, explaining the formation of norvaleroidine on acid hydrolysis. An explanation of the demethylating action of thionyl chloride on valeroidine hydrobromide is also proposed.

VALEROIDINE has been shown (Part I, *J.*, 1937, 1821) to be a mono*iso*valeryldihydroxytropane. The parent tropanediol differed from the known 2 : 3- and 6 : 7-diols but was shown to be identical with the " dioxytropane " isolated from Peruvian coca leaves by Wolfes and Hromatka (*Merck's Jahresber.*, 1933, **47**, 45) and which they suggested to be tropane-3 : 6-diol. In further work (Part III, *J.*, 1940, 1155) the diacetyl and di*iso*valeryl derivatives of the tropanediol were prepared and attempts were made to determine the positions of the free and esterified hydroxyl groups in valeroidine. Oxidation with various reagents in acid aqueous solution gave no positive results, but with potassium permanganate in acetone, besides a small yield of norvaleroidine [compare preparation of nortropine from tropine (Willstätter, *Ber.*, 1896, **29**, 1580), norscopoline from scopoline (Lubold, *Arch. Pharm.*, 1898, **236**, 22), etc.], a new neutral compound was obtained. At that time analysis indicated the formula $C_{13}H_{21}O_4N$ for this compound. On boiling with alcoholic hydrochloric acid the compound was converted into norvaleroidine. This was an unexpected result which could not then be explained.

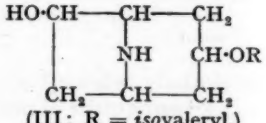
It is now suggested that the oxidation product is an inner urethane (II) formed by elimination of water from a labile carbamic acid (I) initially produced by oxidation of the *N*-methyl group. Formula (II) requires $C_{13}H_{19}O_4N$, with which later analyses were in closer agreement; it would explain the formation of norvaleroidine (III) by elimination of carbon dioxide on acid hydrolysis. It is probable that the rather ill-defined base obtained, along with *iso*valeric acid, on alkaline hydrolysis of the oxidation product was a mixture of nortropane-3 : 6-diol (IV) and the corresponding inner urethane (V).



(I.)

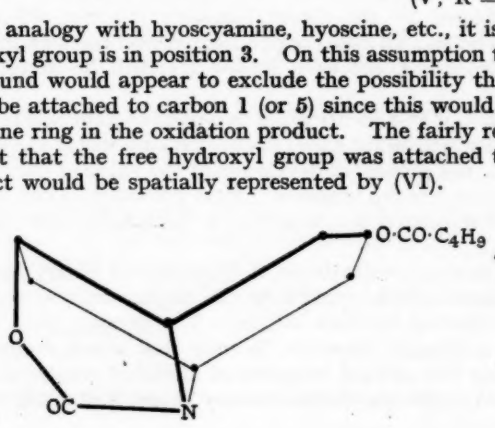


(II; R = *iso*valeryl.)
(V; R = H.)

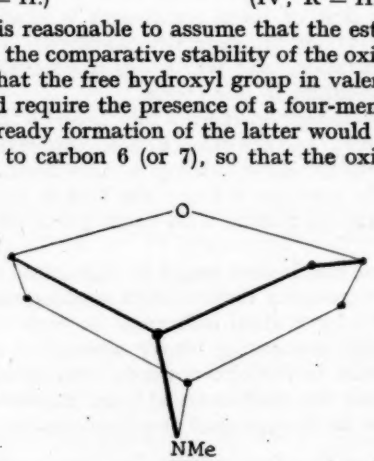


(III; R = *iso*valeryl.)
(IV; R = H.)

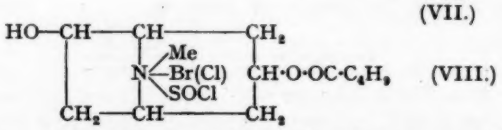
By analogy with hyoscyamine, hyoscine, etc., it is reasonable to assume that the esterified hydroxyl group is in position 3. On this assumption the comparative stability of the oxidation compound would appear to exclude the possibility that the free hydroxyl group in valeroidine could be attached to carbon 1 (or 5) since this would require the presence of a four-membered urethane ring in the oxidation product. The fairly ready formation of the latter would rather suggest that the free hydroxyl group was attached to carbon 6 (or 7), so that the oxidation product would be spatially represented by (VI).



(VI.)



(VII.)



(VIII.)

Wolfes and Hromatka (*loc. cit.*) obtained a 73% yield of " tropene oxide ", in which they postulated the presence of an ether linkage, by treating their tropanediol with a mixture of

phosphorus oxychloride and pentachloride. This compound, more correctly termed desoxyscopoline, can be spatially represented by (VII).

In Part III (*loc. cit.*) attempts to replace the free hydroxyl group in valeroidine by chlorine were also described. These were unsuccessful, but on treating valeroidine hydrobromide (the free base did not give the reaction) with thionyl chloride the curious fact was noted that norvaleroidine was obtained in good yield. It is now suggested that this reaction proceeds through the formation of a labile compound (VIII) which, by loss of methyl chloride (or bromide) and subsequent hydrolysis, yields norvaleroidine (III).

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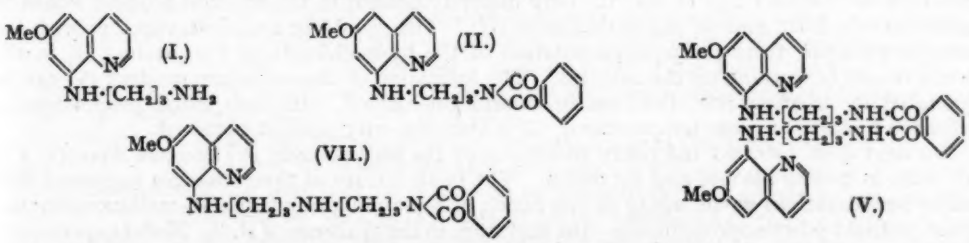
244. *Contributions to the Chemistry of Synthetic Antimalarials. Part IV. Hydrazine Hydrolysis and Radical Exchange Reactions of* N*-Substituted Phthalimides in Relation to the Constitution of the Antimalarial R.*63.

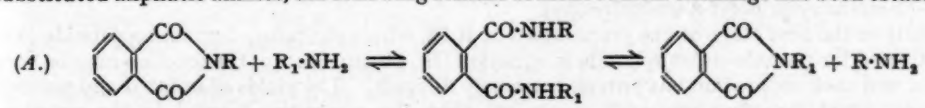
By H. J. Barber and W. R. Wragg.

Hydrazine hydrolysis of *N*-substituted phthalimides has been shown to give the *phthalylhydrazide* salts of the liberated primary amines. Facile radical exchange reactions have been observed between *N*-substituted phthalimides and substituted aliphatic primary amines. The special case of 8-γ-phthalimidopropylamino-6-methoxyquinoline (II) has been studied in detail. The bearing of these reactions on the composition of R.63 is discussed. The antimalarial activity of R.63 can be accounted for on the basis of the 8-γ-aminopropylamino-6-methoxyquinoline (I) dihydrochloride it contains.

Early in 1944, we required 8-γ-aminopropylamino-6-methoxyquinoline (I) in quantity for part of our antimalarial research programme. In preparing this, we encountered certain side reactions relevant to the constitution of the synthetic antimalarial known as R.63 (Robinson and Tomlinson, *J.*, 1934, 1524). This subject had just been reopened by Robinson and his collaborators (*J.*, 1943, 555, 557, 561), who showed that the original constitution ascribed to R.63 was untenable and that most of the feasible alternatives were also excluded. Here was a synthetic drug of confirmed high antimalarial activity (Index 1/64) but of unknown constitution. The hypothesis that the activity was due to the presence, as an impurity, of a small proportion of a still more highly potent antimalarial was an attractive one. The discovery of the side reactions referred to above encouraged this view and indicated the nature of the impurities which might be expected. While our results do not provide absolute proof of the complete composition of R.63 and the source of its activity, they afford strong circumstantial evidence that it is a mixture of a number of products in which the dihydrochloride of (I) is present in sufficient quantity to account for the biological results obtained.



In the synthesis of " antimalarial side chains " by phthalimido-alkylation reactions with substituted aliphatic amines, the following scheme of facile radical exchange has been established:



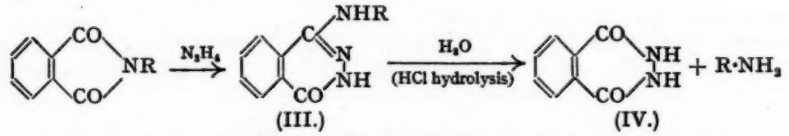
The main factors which determine the end products will be the electronic characteristics of R and R_1, and such relevant properties of their derivatives as solubility in the reagents used or

volatility at the reaction temperature. Examples of (*A*) where R and R_1 = Me, Et, or H have been described recently by Spring and Woods (*J.*, 1945, 625).

The importance to R.63 of the scheme (*A*) first became apparent while studying the hydrazine hydrate hydrolysis of 8-γ-phthalimidopropylamino-6-methoxyquinoline (II).

A number of workers (Baldwin, *J.*, 1929, 2962; Magidson and Bobishev, *J. Gen. Chem. Russia*, 1938, **8**, 912; Beer, *ibid.*, 1939, **9**, 2158; Quin and Robinson *J.*, 1943, 555) had previously used this reaction to prepare (I), their method being based on that of Ing and Manske (*J.*, 1926, 2349) who formulated the hydrolysis as follows:

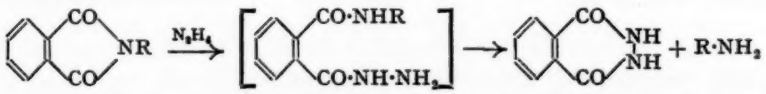
(*B.*)



(III.) (IV.)

We have found that the sparingly soluble intermediate which separates from the reaction mixture has not the structure (III) ascribed to it tentatively by Ing and Manske, but is in fact the *salt* of the acidic phthalylhydrazide (IV) with the liberated amine. It is more probable that the course of the reaction is:

(*C.*)



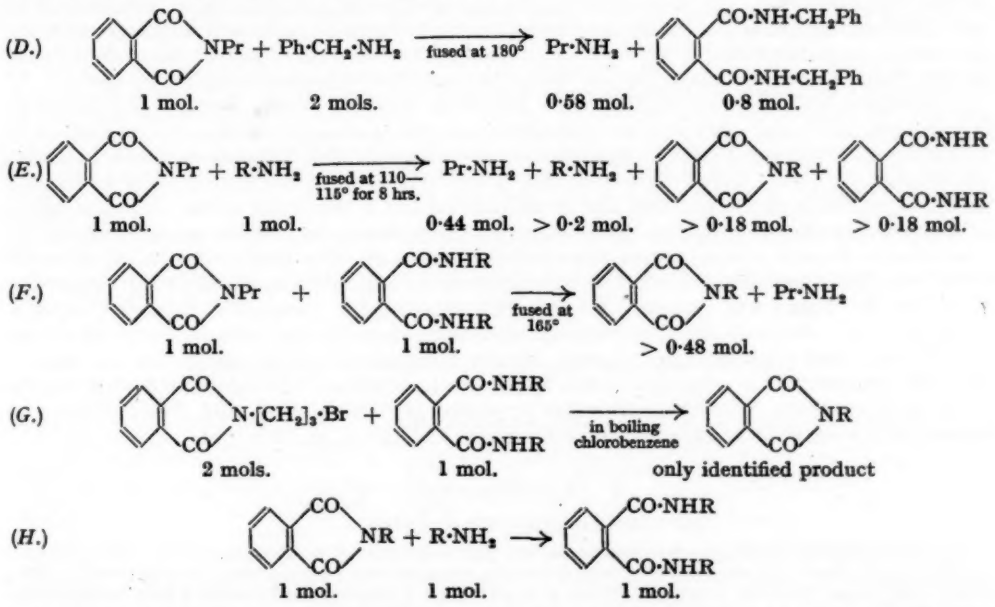
It is clear that this revised conception of the nature of the intermediate (III) suggests modified methods of isolating amines produced by the hydrazine reaction and thus broadens the scope of the method. It is no longer correct to regard the final stage of warming with acid as a hydrolysis of an intermediate such as (III), but as the simple decomposition of a salt by acid. This decomposition can also be effected by alkali, by solvent extraction, or by thermal dissociation. Incidentally, the last procedure provides a ready method of obtaining anhydrous volatile amines where their isolation from the aqueous solutions normally obtained is a matter of some difficulty; application to the laboratory preparation of anhydrous hydrazine will be recorded in a future note.

The intermediate salt we obtained by hydrazine hydrolysis of (II) was dissociated into its components by chloroform extraction and by basification. It was always contaminated by a proportion (dependent on the molar proportion of hydrazine, see Table I) of a secondary product, *phthalobis-[γ-(6-methoxy-8-quinolylamino)propyl]amide* (V). This arose by interaction [scheme (*A*)] between unchanged (II) and free primary amine (I), derived from the partial dissociation in the reaction mixture of its phthalylhydrazide salt. We have studied the acid hydrolysis of the phthalamide (V) under various conditions (Table II) to ascertain the fate of this impurity at the final stage of the Ing and Manske hydrolysis. Under typical conditions complete conversion into an equimolar mixture of (I) and (II) occurred. Thus in a hydrolysis of 1·0 mol. of (II) by the method of scheme (*B*) using 1·0 mol. of hydrazine hydrate, it can be deduced from Tables I and II that the only impurity present in the reaction product would be approximately 0·075 mol. of the phthalimide (II). This would be removed, together with the phthalylhydrazide, from the aqueous solution of the hydrochloride of the product (I) in the normal course of working up the reaction. The formation of the secondary product (V) can be eliminated by treating (II), dissolved in chloroform–alcohol, with two molar proportions of hydrazine hydrate at room temperature; (I) is then the only product obtained.

We next demonstrated the ready formation of the phthalamide (V) directly from (I) and (II), both in boiling alcohol and by fusion. The facile nature of these changes suggested that similar considerations would apply to the fusion of 8-γ-aminopropylamino-6-methoxyquinoline (I) and phthalo-γ-bromopropylimide—the first stage in the synthesis of R.63. Model experiments with some phthalimides and amines, selected for readier separation of the reaction products, confirmed scheme (*A*). These experiments are summarised in the following schemes in which R = γ-(6-methoxyquinolyl-8-amino)propyl.

Clearly in the first stage of the preparation of R.63, where phthalo-γ-bromopropylimide (VI) is substituted for phthalo-*n*-propylimide in equation (*E*), the products of the reaction may be very complex and their separation has proved extremely difficult. The yields of isolated and purified substances must therefore represent much less than the quantities formed in the reaction. From the product of fusing (I) and (VI) by the method of Glen and Robinson (*J.*, 1943, 557) we isolated *in a pure state* the following: 8-γ-phthalimidopropylamino-6-methoxyquinoline

(II) in 5% of the theoretical quantity, 8-γ-aminopropylamino-6-methoxyquinoline (I) in 10% recovery, and a small quantity of 8-γ'-phthalimidopropyl-γ-aminopropylamino-6-methoxyquinoline (VII) monohydrobromide. Since our object was to identify the highly active component responsible *ex hypothesi* for the activity of R.63, we did not attempt quantitative separation of the mixture but turned our attention instead to the synthesis of compounds deduced from the application of scheme (*A*).


(D.)
NPr + Ph·CH₂·NH₂ → (fused at 180°) Pr·NH₂ + CO·NH·CH₂Ph / CO·NH·CH₂Ph
1 mol. 2 mols. 0·58 mol. 0·8 mol.
(E.)
NPr + R·NH₂ → (fused at 110—115° for 8 hrs.) Pr·NH₂ + R·NH₂ + NR + CO·NHR / CO·NHR
1 mol. 1 mol. 0·44 mol. > 0·2 mol. > 0·18 mol. > 0·18 mol.
(F.)
NPr + CO·NHR / CO·NHR → (fused at 165°) NR + Pr·NH₂
1 mol. 1 mol. > 0·48 mol.
(G.)
N·[CH₂]₃·Br + CO·NHR / CO·NHR → (in boiling chlorobenzene) NR
2 mols. 1 mol. only identified product
(H.)
NR + R·NH₂ → CO·NHR / CO·NHR
1 mol. 1 mol. 1 mol.

(II) doubtless appeared as the result of a reaction, type (*E*), from which we inferred that the highly reactive bifunctional compound, γ-bromopropylamine (VIII), was liberated simultaneously with (II). (VIII) could undergo self-condensation to 1 : 5-diaza*cyclo*octane dihydrobromide (IX) or react in many ways with the various components of the melt. However, both the hydrobromide of (VIII) (Gabriel, *Ber.*, 1888, **21**, 2669) and (IX) (Buhle, Moore, and Wiselogle, *J. Amer. Chem. Soc.*, 1943, **65**, 29) have been found devoid of antimalarial activity.

As molecular proportions of the reagents (I) and (VI) are used in this fusion, the recovery of 10% of unchanged (I) indicated that a similar quantity of phthalo-γ-bromopropylimide (VI) might remain unchanged in the fusion product. This would react during the second stage of the preparation of R.63 (treatment of the crude fusion melt with alcoholic hydrazine hydrate followed by warm dilute hydrochloric acid) giving a variety of products. Accordingly, pure (VI) was submitted to the sequence of hydrazine treatment (using various molar proportions of hydrazine) and acid " hydrolysis ", but the total basic product derived was always inactive.

Lastly the identification of the " normal " product (VII) of the fusion reaction of (I) and (VI) in the crude melt indicated that some 8-γ'-aminopropyl-γ-aminopropylamino-6-methoxyquinoline trihydrochloride would appear in R.63.

Being impressed by the fact that most of the physical change in the fusion reaction took place during the first few minutes, we studied the rate at which the free amino-group of (I) reacted. Table III summarises the results of some Van Slyke nitrogen determinations and shows their relation to the quantities of the various products proved to be present in the melt after various times of fusion. It is noteworthy that the proportion of primary amine (Van Slyke) drops to approximately 30% of its initial value in the first five minutes of fusion and remains at this value even after the seven hours specified by Glen and Robinson (*loc. cit.*).

The complex nature of the first reaction in the preparation of R.63 made it apparent that alcoholic hydrazine hydrate treatment of the crude product could only add to its complexity. We did not therefore proceed to attempt to separate R.63 into its components. However, on the evidence submitted here R.63 would obviously contain at least 10% of unchanged (I), together with a further proportion of (I) (> 5%) formed when the phthalimide (II) present in the melt was treated with hydrazine hydrate. If the Van Slyke figure for N were taken as a

measure of the amine (I) present in the fusion product, a reasonable assumption, then the final R.63 could be calculated to contain > 35% of the possible quantity of the amine (I).

Results obtained in the Biological Laboratories, May & Baker Ltd., indicate that the antimalarial activity and toxicity of R.63 are in general accord with the chemical evidence that upwards of 30% of (I) is present. It should be emphasised, however, that extreme caution is necessary in interpreting the results obtained on a mixture, since the biological properties may be far from additive. The presence of a small proportion of a highly active substance is still not definitely excluded. A fuller discussion of the biological results will appear elsewhere in due course, together with a report on the antimalarial evaluation of phthalobis-[γ-(6-methoxy-8-quinolylamino)propyl]amide (V) and 8-*γ-phthalamidopropylamino-6-methoxyquinoline*.

Addendum.—Publication of this work has been delayed largely because British Patent Application 17071/44, covering the preparation of the phthalamide (V), was placed on the secret list. An independent investigation of the constitution of R.63 has been described recently by Mosher (*J. Amer. Chem. Soc.*, 1946, **68**, 1565). We had, however, followed a somewhat different approach to the problem and overlap in results is restricted to the following points:

Mosher is in agreement that R.63 (as prepared by Robinson and his co-workers) contains considerable 8-γ-aminopropylamino-6-methoxyquinoline (I) dihydrochloride (R.36) and some 4% of 8-γ-phthalimidopropylamino-6-methoxyquinoline (II), although he does not explain how the latter compound was formed. He has demonstrated the presence of a larger proportion (> 20%) of 8-γ′-aminopropyl-γ-aminopropylamino-6-methoxyquinoline trihydrochloride (R.120) than that reported here. Lastly, Mosher foreshadows our elucidation of the nature of the intermediate which separates in the hydrazine hydrolysis of *N*-substituted phthalimides.

A brief summary of the present paper appeared in *Nature* (1946, **158**, 514). Spring and Woods have since added further evidence for scheme (*A*) (*ibid.*, p. 754).

Experimental.

(Melting points are corrected.)

8-γ-Phthalimidopropylamino-6-methoxyquinoline (II).—8-Amino-6-methoxyquinoline (696 g.) (Barber and Wragg, *J.*, 1946, 612) was refluxed with 0·5 molar proportion of phthalo-γ-bromopropylimide (536 g.) in chlorobenzene (2 l.) for 12 hours. After a short delay, 8-amino-6-methoxyquinoline hydrobromide commenced to separate. This salt (404 g.; 76%) was collected from the cold reaction mixture and the filtrate diluted with alcohol (6 l.); 8-γ-phthalimidopropylamino-6-methoxyquinoline then separated as yellow felted needles. The product was collected after 24 hours, washed with light petroleum (2 l.)–alcohol (750 c.c.), and dried at 40°/11 mm., giving 403 g. (56%), m. p. 99—101°. The chlorobenzene–alcohol liquors were treated with excess of concentrated hydrochloric acid, and the precipitated orange hydrochloride was removed and washed with alcohol (500 c.c.). The damp salt (344 g.) was suspended in boiling alcohol (5 l.) and treated with a small excess of concentrated ammonia. 8-γ-Phthalimidopropylamino-6-methoxyquinoline (104 g.) crystallised, making a total yield of 70%. No 8-bis-(γ-phthalimidopropyl)amino-6-methoxyquinoline was obtained as a by-product under these conditions (cf. Glen and Robinson, *loc. cit.*; Mosher, *loc. cit.*).

8-γ-Aminopropylamino-6-methoxyquinoline (I).—(a) *Hydrolysis of* (II) *in cold chloroform–alcohol using 2·25 mols. of hydrazine hydrate.* 8-γ-Phthalimidopropylamino-6-methoxyquinoline (7·22 g.) dissolved in chloroform (50 c.c.) and alcohol (50 c.c.) was treated with hydrazine hydrate (4·5 c.c., 50% w/v aqueous solution). After 3 hours at room temperature a gelatinous white precipitate began to separate. After 4 days the solvents were removed at 40°/20 mm. and the residue shaken mechanically (2 hours) with a mixture of 2N-ammonia (30 c.c.), water (40 c.c.), and chloroform (70 c.c.). A small quantity of insoluble material (*ca.* 0·5 g.) was dissolved separately by warming with chloroform–ammonia solution and returned to the main bulk. The chloroform layer (*A*) was extracted with four portions of N-acetic acid (20 c.c.) which were bulked, basified with concentrated ammonia, and then exhaustively extracted with ether. This extract on distillation in a bulb tube (air-bath at 180°) at 0·01 mm. gave 8-γ-aminopropylamino-6-methoxyquinoline (4·1 g., 89%), $n_D^{24°}$ 1·637, converted into carbamate derivative, m. p. 113—116°. The chloroform (*A*) was evaporated to dryness, leaving a negligible dark red residue (0·2 g.). The aqueous ammoniacal layer, precipitated with concentrated hydrochloric acid, yielded 2·98 g. (92%) of phthalylhydrazide, m. p. 342—344°.

(b) *Hydrolysis of* (II) *in boiling alcohol with various proportions of hydrazine hydrate.* Hydrazine hydrate (40 c.c., 50% w/v aqueous solution; 0·8 mol.) was added to a solution of 8-γ-phthalimidopropylamino-6-methoxyquinoline (180 g.) in boiling alcohol (1·5 l.) and the mixture refluxed for 3 hours. The alcohol was removed under reduced pressure from the suspension of cream insoluble product, and the residue vigorously shaken with 2N-ammonia (500 c.c.), diluted with water (1 l.), and chloroform (2·5 l.). The aqueous alkaline layer was separated and acidified with concentrated hydrochloric acid; phthalylhydrazide separated (56 g.), m. p. 342—344°.

The chloroform layer was concentrated under reduced pressure to 700 c.c. and diluted with an equal volume of dry ether. *Phthalobis-[γ-(6-methoxy-8-quinolylamino)propyl]amide* (V) separated (44 g.), m. p. 170—174°, crystallising from chloroform–methanol as tiny brown needles, m. p. 177—179° (Found: C, 68·7; H, 6·3; N, 14·0; OMe, 11·0; *M* (ebulliscopic in chloroform), 600. $C_{34}H_{34}O_4N_8$ requires C, 68·9; H, 6·1; N, 14·2; OMe, 10·5%; *M*, 592). (V) was converted into the *hydrochloride*, m. p. 208—210° by treatment of a warm solution in chloroform–methanol with concentrated hydrochloric acid

(Found: N, 12·6; Cl, 10·6. $C_{34}H_{36}O_4N_8,2HCl$ requires N, 12·6; Cl, 10·7%). This hydrochloride was readily reconverted into the base by suspension in a large volume of cold water.

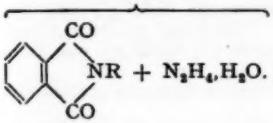
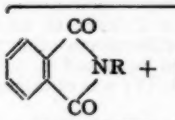
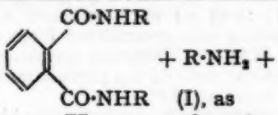
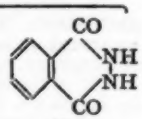
The liquors from the separation of crude (V) above were evaporated to dryness under reduced pressure and the oily residue taken up in dry ether (1 l.). Carbon dioxide was passed, very slowly at first, into the filtered bright ethereal solution, precipitating the *carbamate* derived from (I) (63 g.) as a white powder, m. p. 112—114° [Found: C, 64·2; H, 7·0; N, 16·8. $(C_{13}H_{17}ON_3)_2CO_2$ requires C, 64·0; H, 6·76; N, 16·6%]. When a solution of the carbamate in warm methanol was treated with a small excess of concentrated hydrochloric acid the corresponding *dihydrochloride*, crystallising from methanol–ether in short orange needles, was obtained (96%). Drying over potash in a vacuum gave the anhydrous salt (cf. Beer, *loc. cit.*), m. p. 244—246° with slight previous shrinking from about 230° [Purification of many samples failed to give material, m. p. 251—252° (cf. Baldwin, *loc. cit.*; Beer, *loc. cit.*)] (Found: N, 13·7; Cl, 23·5. Calc. for $C_{13}H_{17}ON_3,2HCl$: N, 13·8; Cl, 23·4%). The free base (I) was prepared in 96% yield by dissolving the carbamate in a small excess of dilute hydrochloric acid at 80°, removing any dissolved carbon dioxide with a rapid stream of nitrogen for 10 minutes, basifying with concentrated aqueous ammonia, and extracting the liberated base with ether. Distillation of the residue on removal of the ether gave (I) as a single fraction, b. p. 160°/0·01 mm., a viscous yellow oil, $n_D^{23°}$ 1·637 (Found: C, 67·5; H, 7·4; N, 18·05. Calc. for $C_{13}H_{17}ON_3$: C, 67·5; H, 7·4; N, 18·2%), stored under an atmosphere of hydrogen. On long standing this sample solidified to a waxy solid, m. p. 37—38°.

In the experiment below where unchanged phthalimide (II) was recovered, this was isolated from the ethereal liquor after the precipitation and removal of the carbamate of (I).

The above experimental details exemplify the method of separation employed to obtain the results summarised in Table I.

TABLE I.

Reaction of the phthalimide (II) *with hydrazine hydrate.*

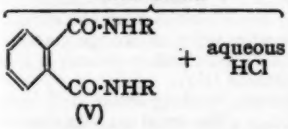
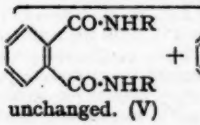
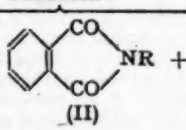
Reactants.			Products.			
 (II)	N_2H_4,H_2O.	Time in boiling alcohol.	 unchanged (II)	 (V)	+ $R{\cdot}NH_2$ + (I), as carbamate.	 (IV)
1·0 mol.	1·0 mol.	2 hrs.	none	0·075 mol.	0·57 mol.	Theoretical quantity
1·0 mol.	0·8 mol.	4 hrs.	none	0·15 mol.	0·5 mol.	,,
1·0 mol.	0·5 mol.	10 hrs.	0·3 mol.	0·16 mol.	0·23 mol.	,,

[R = γ-(6-methoxyquinolyl-8-amino)propyl.]

The products obtained, when the phthalamide (V) was treated with aqueous hydrochloric acid under various conditions, were separated and identified by means very similar to those described in the case of Table I. These results are summarised in Table II.

TABLE II.

Reaction of the phthalamide (V) *with acid.*

Reactants.		Conditions.	Products.		
 (V)	+ aqueous HCl		 unchanged. (V)	+  (II)	+ $R{\cdot}NH_2$. (I) as carbamate.
2 g.	90 c.c., 10%	1 hr. reflux	none	0·8 g.	trace
2 g.	30 c.c., 2N	30 mins. at 95°	none	1·05 g.	0·6 g.
2 g.	30 c.c., N	15 mins. at 95°	0·75 g.	0·57 g.	0·17 g.
2 g.	30 c.c., N	15 mins. at 70°	1·75 g.	none	trace

[R = γ-(6-methoxyquinolyl-8-amino)propyl.]

Model Experiments.—(a) *Exemplification of scheme* (C) *where* R = *benzyl.* Phthalobenzylimide (23·7 g.) was suspended in alcohol (200 c.c.), boiling under reflux, and hydrazine hydrate (10 c.c., 50% w/v aqueous solution; 1·0 mol.) added. After 2 hours the reaction mixture was cooled and the white crystalline product collected (21·3 g.). After being dried in the steam-oven for 1 hour this material analysed for the anhydrous phthalylhydrazide (IV) *salt* of benzylamine, m. p. 326—346° (Found: C, 66·8; H, 5·4; N, 15·5. $C_8H_6O_2N_2,C_7H_9N$ requires C, 67·0; H, 5·6; N, 15·6%). 2 G. of this salt were dissociated by one crystallisation from alcohol (200 c.c.); phthalylhydrazide alone separated, m. p. 342—346° (Found: C, 59·6; H, 4·0; N, 17·5. Calc. for $C_8H_6O_2N_2$: C, 59·3; H, 3·7; N, 17·3%). Dissociation was also effected by heating the salt (5·4 g.) at 120—140°/0·05 mm. for 3 hours. The

distillate, collected in a solid carbon dioxide–acetone cooled receiver, was anhydrous benzylamine (1·66 g.; 78%) (Found: *M*, by titration, 107. Calc. for C_7H_9N: *M*, 107).

(b) *Exemplification of scheme* (*D*). Phthalo-*n*-propylimide (10 g.) and benzylamine (11·4 g.; 2 mol.) were fused in a distillation flask fitted with a Vigreux column. The melt was slowly heated to 180°. The distillate (b. p. 49°), collected in a cooled receiver, was anhydrous propylamine (1·8 g., 59%) contaminated by a small proportion of benzylamine. The residue, crystallised twice from chloroform, was phthalo-*NN'*-dibenzylamide, m. p. 176—178° (Tingle and Lovelace, *Amer. Chem. J.*, 1907, **38**, 651, give m. p. 178—179°).

(c) *Exemplification of scheme* (*E*). 8-γ-Aminopropylamino-6-methoxyquinoline (2·2 g.) was fused with phthalo-*n*-propylimide (1·89 g.) for 8 hours at 110—115°. The *n*-propylamine (44%) evolved from the melt was removed in a slow stream of hydrogen which was subsequently scrubbed with standard acid. The fusion product was dissolved in methanol (40 c.c.). On cooling, the phthalamide (V) separated, 1·06 g., m. p. 157—171°. Recrystallisation from chloroform–methanol gave 0·9 g., m. p. 176—178°; mixed m. p. with authentic material was 175—178°. On standing, the liquors from the crude phthalamide (V) precipitated the phthalimide (II) (0·64 g.) (*A*), m. p. 97—99°, characterised by mixed m. p. 100—101° with authentic material after recrystallisation from methanol. The methanol liquors from (*A*) were concentrated, and the residue dissolved in ether was treated with carbon dioxide, precipitating the carbamate of the amine (I) (0·5 g.), m. p. 112—116°.

(d) *Exemplification of scheme* (*F*). An equimolar mixture of the phthalamide (V) (5·9 g.) and phthalo-*n*-propylimide (1·9 g.) were fused at 165° for 1 hour, during which time *n*-propylamine was evolved. The fusion product was dissolved in alcohol (50 c.c.) from which 3·5 g. (48%) of bulky yellow needles separated, m. p. 84—100°. Recrystallisation from alcohol gave the phthalimide (II) (3·2 g.), m. p. 99—101°, characterised by mixed m. p. with an authentic sample.

(e) *Exemplification of scheme* (*G*). The phthalamide (V) (1·18 g.) was refluxed for 10 hours in chlorobenzene (20 c.c.) with phthalo-γ-bromopropylimide (1·07 g.). The hydrochloride precipitated from the mixture by alcoholic hydrogen chloride was crystallised twice from alcohol and then converted in aqueous methanol into the base, long bulky yellow needles from methanol (0·2 g.), m. p. 99—101°, shown to be the phthalimide (II) by mixed m. p.

(f) *Exemplification of scheme* (*H*). (i) Equimolar proportions of the amine (I) (2·31 g.) and the phthalimide (II) (3·61 g.) were refluxed for 1 hour in alcohol (70 c.c.). The total product which separated on cooling was crystallised from chloroform–ether; the phthalamide (V) (2·05 g.) was thus obtained, m. p. 173—176° (identity confirmed by mixed m. p.).

(ii) A theoretical yield of the phthalamide (V) was obtained when the above reaction was carried out by fusion for 1 hour at 115°.

(iii) A 70% yield of the phthalamide (V) was similarly obtained from the fusion of the amine (I) (5·1 g.; 2 mols.) and phthalic anhydride (1·5 g.) at 115° for 1 hour.

(iv) A theoretical yield of phthalo-*NN'*-dibenzylamide was similarly obtained by fusion of equimolecular quantities of phthalobenzylimide and benzylamine at 120° for 1½ hours.

*First Stage of the Preparation of R.*63. *Separation of the Reaction Products of the Fusion of* 8-γ-*Aminopropylamino*-6-*methoxyquinoline* (I) *with Phthalo*-γ-*bromopropylimide* (VI).—The identification of unchanged (I) and the phthalimide (II) as products of this reaction has been confirmed at least twice, both after 15 minute and 7 hour fusions. The following are typical experiments:

(a) *Method of fusion.* Equimolar proportions of (I) (6 g.) and (VI) (7 g.) were mixed by rotation of the reaction flask, closed by a calcium chloride tube, and immersed in an oil-bath at 115°. The mixture fused to a mobile liquid which rapidly thickened to a red-brown glass.

(b) *Isolation of* 8-γ-*phthalimidopropylamino*-6-*methoxyquinoline* (II). The glassy product from a 7 hour fusion as in (a) was dissolved in glacial acetic acid (15 c.c.) with mechanical shaking (10 hours). The orange-brown precipitate which separated was filtered from the viscous red liquor, washed with three portions of glacial acetic acid (5 c.c.) and then ether, giving 1·7 g., m. p. 190—200°. This was repeatedly recrystallised from methanol until the orange hydrobromide obtained (0·98 g.), m. p. 214—220°, was sufficiently pure to yield 0·3 g. of phthalimide (II), m. p. 102—103° (identity confirmed by mixed m. p.), on treatment with ammoniacal methanol. By dilution with water and recrystallisation of the precipitate, a further 0·1 g., m. p. 100—103°, of the phthalimide (II) was isolated from the mother liquor. The original acetic acid liquors were stored at 0° (2 days) when a further 0·6 g. of orange material separated. This crystallised from methanol giving 0·35 g., m. p. 220—225°, which on conversion into the base (0·09 g.) was characterised by mixed m. p. 101—103° as the phthalimide (II).

(c) *Isolation of* 8-γ-*aminopropylamino*-6-*methoxyquinoline* (I). The fusion product from a 7 hour reaction as (a) was dissolved with mechanical shaking in chloroform (50 c.c.). The solution was shaken with 2N-ammonia (12 c.c.) and water (20 c.c.). The chloroform layer was then extracted with four 2 c.c. portions of 2N-acetic acid in water (20 c.c.) until the last extract was acid (litmus). The combined extracts were counter-extracted (chloroform) and then basified slowly with 2N-ammonia in the presence of ether (500 c.c.). The aqueous layer was then made strongly alkaline with concentrated ammonia and saturated with salt. The dried (K_2CO_3) ether layer was evaporated and distilled in a bulb tube (air-bath up to 200°) at 0·01 mm. About half the residue distilled, yielding a light brown oil, 2·0 g., $n_D^{24°}$ 1·631. This was taken up in ether and converted into the carbamate of (I) (0·7 g., 10% recovery), m. p. 100—108°, decomposing in a bulb tube to give pure (I) (0·5 g.), $n_D^{23°}$ 1·636, reconverted into carbamate derivative, m. p. 109—115° (mixed melting point with authentic material 113—116°).

(d) *Isolation of* 8-γ′-*phthalimidopropyl*-γ-*aminopropylamino*-6-*methoxyquinoline* (VII). The product from a 7 hour fusion, as (a) was dissolved in pyridine (25 c.c.). The brown oil precipitated with water (300 c.c.) was twice extracted by boiling with a supernatant layer of ether (100 c.c.). The residue separated by decantation was dissolved in methanol (100 c.c.) and diluted with an equal volume of ether. The precipitated gum solidified on standing. The solid was collected and recrystallised twice from methanol, forming long rectangular light brown plates, m. p. 174—177°, which proved to be 8-γ′-*phthalimidopropyl*-γ-*aminopropylamino*-6-*methoxyquinoline monohydrobromide* (Found: C, 57·4; H, 5·1; N, 11·0; Br, 15·8. $C_{24}H_{24}O_3N_4$,HBr requires C, 57·7; H, 5·4; N, 11·2; Br, 16·1%). We con-

cluded that this product was not 8-γ-aminopropylamino-6-methoxy-1-γ-phthalimidopropylquinolinium bromide, or 8-γ-aminopropyl-γ-phthalimidopropylamino-6-methoxyquinoline hydrobromide, compounds of the same empirical formula, because no primary amine group could be detected in a micro-Van Slyke determination, for which we are indebted to Miss P. Garwood of Imperial College, S.W. 7.

(e) *Typical analytical experiment in outline.* The product from a 15 minute fusion, as in (a), was dissolved in alcohol (50 c.c.). The solution was slowly added to well-stirred ether (300 c.c.). The milky product was shaken with 100 c.c. water and then extracted with N-hydrochloric acid (20 c.c.). The bright ether layer was dried (K_2CO_3) and evaporated to give 1·3 g. (18% recovery) of unchanged phthalo-γ-bromopropylimide (VI), m. p. 69—72° The bulked aqueous extracts were basified with 50% sodium hydroxide and the total bases taken up into chloroform (150 c.c.) (*A*). This was extracted with 2N-acetic acid (25 c.c.) in water (50 c.c.), and the extracted material taken as base into ether. This dried (K_2CO_3) ether extract yielded the carbamate of (I) (1·0 g., 16% recovery). The chloroform (*A*) was next removed and the residue converted into hydrochloride (*B*) which was crystallised from alcohol. The insoluble hydrochloride of the phthalimide (II) (1·6 g., 15%) was first obtained. This was repeatedly crystallised from methanol, and, when sufficiently pure, converted into base confirmed to be (II) by m. p. and mixed m. p. The more soluble hydrochloride in the mixture (*B*) was crystallised from alcohol–ether many times without a pure substance being definitely characterised, although a N : Cl ratio of 2·07/1 indicated 8-γ′-phthalimidopropyl-γ-aminopropylamino-6-methoxyquinoline (VII) dihydrochloride.

The above results are summarised in Table III, together with Van Slyke estimations for primary amino-group on the products of fusions [as (a)] of varying duration.

TABLE III.

*R.*63 *fusion. Progress of reaction.*

Duration of fusion.....	Nil.	5 mins.	15 mins.	7 hrs.
Van Slyke estimation of N present as primary amino-group (%)	6·4, 6·3*	2·1	—	2·4
Proportion of amine (I) recovered unchanged (%)	—	—	16	10
Proportion of phthalimide (VI) recovered unchanged (%)	—	—	18	—
Proportion of theoretically possible phthalimide (II) actually isolated as crude hydrobromide (%)	—	—	15	22†

* Amine (I) requires 6·06%. † 5% as pure base.

*Preparation of R.*63 *for Antimalarial Test.*—The procedure of Glen and Robinson (*loc. cit.*) was exactly followed [Found on our sample of R.63 : N as primary amino-group (Van Slyke), 4·85. Calc. for amine (I) dihydrochloride, 4·6. Calc. for 8-γ′-aminopropyl-γ-aminopropylamino-6-methoxyquinoline trihydrochloride, 3·5%].

8-*Bis*-(γ-*phthalimidopropyl*)*amino*-6-*methoxyquinoline.*—8-γ-Phthalimidopropylamino-6-methoxyquinoline (20 g.) was fused with exclusion of moisture with phthalo-γ-bromopropylimide (32 g.) for 12 hours at 120°. The red glassy product was dissolved in methanol (200 c.c.), and an orange hydrobromide (20 g.) crystallised out. This was converted into base in methanol–2N-ammonia. 8-Bis-(γ-phthalimidopropyl)amino-6-methoxyquinoline crystallised from pyridine–methanol, m. p. 165—167° (13 g., 43%) (cf. Quin and Robinson, *loc. cit.*).

8-γ-*Phthalamidopropylamino*-6-*methoxyquinoline.*—8-γ-Phthalimidopropylamino-6-methoxyquinoline (20 g.) was added to a boiling solution of potassium hydroxide (13·8 g.) in alcohol (275 c.c.). After 30 minutes the mixture was cooled to 0° and almost neutralised with 2N-hydrochloric acid. The precipitated salt was just dissolved by adding water (200 c.c.) and the alcohol removed at 30 mm. The remaining liquor (charcoaled) was just acidified (litmus) cold with glacial acetic acid. The precipitated *product* was crystallised from aqueous methanol and dried over phosphoric oxide at 10 mm. (Found : C, 63·7; H, 6·1; N, 10·7; *M*, by titration, 390. $C_{21}H_{21}O_4N_3,H_2O$ requires C, 63·5; H, 5·8; N, 10·6%; *M*, 397). The loss in weight at 100° on this hydrated acid (Found : 9·2. $C_{21}H_{21}O_4N_3,H_2O$ requires 4·54%) indicated that both dehydration and ring closure had occurred, giving the phthalimide (II). This was confirmed by m. p. 101—103° and mixed m. p. 101—104° with authentic material after one crystallisation from methanol.

We are indebted to Mr. S. Bance, B.Sc., A.R.I.C., for the semi-microanlayses, and to the Directors of Messrs. May and Baker Ltd. for permission to publish these results.

RESEARCH LABORATORIES,
MAY & BAKER LTD., DAGENHAM, ESSEX.

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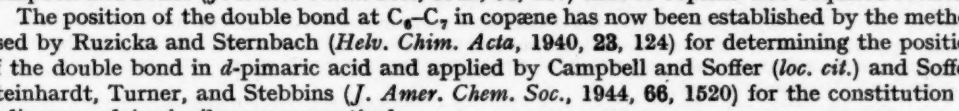
245. *The Constitution of Copæne.*

By Lindsay H. Briggs and William I. Taylor.

The constitution of copæne has been elucidated on the basis of the following sequence of reactions. Perbenzoic acid yields the oxide, converted by methylmagnesium iodide into the corresponding methylcarbinol which after dehydration and dehydrogenation furnishes the known compound, 1 : 6 : 7-trimethyl-4-*iso*propylnaphthalene.

The tricyclic sesquiterpene copæne is a comparatively rare constituent of essential oils, and so far it has only been detected in the oils of *Oxystigma mannii* (Schimmel's Report, 1914, April, p. 48), *Sindora wallichii* (Henderson, McNab, and Robertson, *J.*, 1926, 3077), *S. inermis* (Huzita, *J. Chem. Soc. Japan*, 1941, **62**, 431), *Dysoxylum fraseranum* (Penfold, *J. Proc. Roy. Soc. New South Wales*, 1928, **61**, 337) and *Cedrela toona* (Pillai and Rao, *J. Soc. Chem. Ind.*, 1931, **50**, 220T). More recently it has been identified by Briggs and Sutherland (forthcoming publication) in the oil of the New Zealand tree, *Phyllocladus trichomanoides*, the source for the present investigation.

From the molecular refraction, the formation of a dihydro-derivative, and the oxidation by ozone or potassium permanganate to a monobasic ketonic acid, copæne ketonic acid, $C_{15}H_{24}O_3$, copæne was shown by Semmler and Stenzel (*Ber.*, 1914, **47**, 2555) to be tricyclic with one ethylene linkage. Since it also gave *l*-cadinene dihydrochloride with hydrogen chloride it must contain the cadinene skeleton and a *cyclo*propane ring, later confirmed by Henderson *et al.* (*loc. cit.*) by dehydrogenation with sulphur to cadalene. By further oxidation of copæne ketonic acid with sodium hypobromite, Semmler and Stenzel obtained a dibasic acid, copænedicarboxylic acid, $C_{12}H_{18}O_4$ (*vide infra*), apparently by the elimination of an *iso*propyl group. The provisional formula (I) suggested by Semmler and Stenzel was changed to (II) by Henderson *et al.* in view of the structure (III) proposed by Ruzicka and Stoll (*Helv. Chim. Acta*, 1924, **7**, 84) for cadinene.



(I.) (II.) (III.) (IV.)

In view of the revised structure for cadinene (IV) put forward on a firm experimental basis by Campbell and Soffer (*J. Amer. Chem. Soc.*, 1942, **64**, 417) that of copæne also required revision.

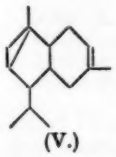
The position of the double bond at C_6–C_7 in copæne has now been established by the method used by Ruzicka and Sternbach (*Helv. Chim. Acta*, 1940, **23**, 124) for determining the position of the double bond in *d*-pimaric acid and applied by Campbell and Soffer (*loc. cit.*) and Soffer, Steinhardt, Turner, and Stebbins (*J. Amer. Chem. Soc.*, 1944, **66**, 1520) for the constitution of cadinene and *iso*zingiberene respectively.

Copæne was converted quantitatively into the oxide by the action of perbenzoic acid. On distillation in high vacuum, however, three fractions were obtained, indicating that some isomerisation to the ketone or fission of the *cyclo*propane ring had occurred. Since the isomeric ketone should give the same product ultimately as the oxide, the combined distillate was treated with excess of methylmagnesium iodide and the resultant methylcarbinol dehydrated with formic acid. Dehydrogenation with palladised charcoal failed to yield an aromatic hydrocarbon, but this was formed with selenium. The dehydrogenation products, after being washed with alkali, were distilled, small fractions being taken off empirically and converted into picrates. From two fractions the picrate of 1 : 6 : 7-trimethyl-4-*iso*propylnaphthalene was obtained after repeated crystallisation, the purest specimen having m. p. 121—122°. Campbell and Soffer (*loc. cit.*) record m. p. 122—123° for their synthetic material. The double bond in copæne must therefore be in the 6—7 position.

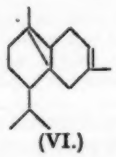
From the alkaline washings of the dehydrogenation product a crystalline *naphthol*, $C_{15}H_{18}O$, was obtained (picrate, trinitrobenzoate) which is probably the previously unknown 7-hydroxy-1 : 6-dimethyl-4-*iso*propylnaphthalene arising from the dehydrogenation of unmethylated copæne oxide or the isomeric ketone. We hope to report later on this compound.

Since copæne forms *l*-cadinene dihydrochloride with hydrogen chloride, the three-membered ring must have one point of attachment at C_1 and the other at C_3 (V) or C_{10} (VI). If the latter, then dehydrogenation should yield an azulene as well as cadalene as in the case of ledene

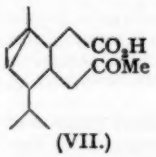
(Komppa and Nyman, *Compt. rend. Trav. Lab. Carlsberg*, 1938, **22**, 272) or azulene alone as in aromadendrene (Radcliffe and Short, *J.*, 1938, 1200). Since no trace of azulene is obtained from copæne the three membered ring must be at C_1–C_3 and copæne must be formulated as (V).



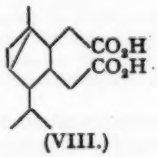
(V.)



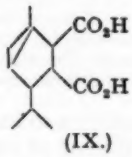
(VI.)



(VII.)



(VIII.)



(IX.)

The copæne ketonic acid, $C_{15}H_{24}O_3$, of Semmler and Stenzel must now be revised to (VII), and the dibasic acid, copænedicarboxylic acid, obtained on sodium hypobromite oxidation, is more probably the normal product (VIII), $C_{14}H_{22}O_4$, rather than (IX) $C_{13}H_{18}O_4$, with which, however, the analytical figures agree.

Experimental.

The copæne used in these experiments was repeatedly fractionated, finally through a 20 plate column, and then had the following constants: b. p. 114—114·5°/10 mm.; $d_4^{25°}$ 0·9055 (constant); $n_D^{25°}$ 1·4880—1·4895; $[\alpha]_D^{13·5°}$ − 0·44° to + 1·20°; it had been identified by Briggs and Sutherland (*loc. cit.*) by the formation of *l*-cadinene dihydrochloride with hydrogen chloride, dehydrogenation to cadalene with palladised charcoal, and oxidation to copæne ketonic acid, characterised as the semicarbazone, m. p. 222°, and the semicarbazone of its methyl ester, m. p. 194—196°.

Copæne Oxide.—A solution of copæne (11·1 g.) in chloroform (200 c.c.) was added to a twofold excess of perbenzoic acid in chloroform (300 c.c.) at 6° and left overnight. Titration of an aliquot portion against standard thiosulphate solution after addition of potassium iodide then showed that reaction was complete. The chloroform solution, after being washed with sodium carbonate and sodium thiosulphate solutions, yielded a viscous colourless oil (11·9 g.), separated by distillation into the following fractions: (1) b. p. 112—120°/0·5 mm., 4·09 g.; (2) b. p. 95—105°/0·03 mm., 2·24 g.; (3) b. p. 127—130°/0·05 mm., 1·37 g.

Methylation and Dehydration.—The combined fractions (7·3 g.) in dry ether (30 c.c.) were slowly added to an ethereal solution of methylmagnesium iodide (3 molal excess), and after the first action had ceased the mixture was refluxed for 30 hours. After decomposition with saturated ammonium chloride solution the reaction mixture was extracted with ether, and the extract, after being washed with brine containing sodium carbonate, then with water, and dried (Na_2SO_4), yielded on distillation of the ether a syrupy product (6·43 g.) in 82% yield. This was boiled under reflux with formic acid (15 c.c.) for 15 minutes and, after addition of water, the product was isolated through light petroleum; yield 5·97 g.

Dehydrogenation.—The dehydrated oil (1·43 g.) and selenium (2·08 g.) were heated slowly to 200° until water ceased to be evolved, the temperature was then maintained at 220° for 16 hours and at 300° for a further 9 hours. The product was extracted with light petroleum, and the solution washed with sodium hydroxide solution and water, and dried; after removal of the solvent 0·864 g. of a slightly fluorescent oil was obtained. On distillation at 10 mm. (bath temperature 120°) five fractions were obtained weighing successively 0·2286 g., 0·0987 g., 0·0736 g., 0·1466 g., and 0·0411 g., leaving 0·2090 g. of a residual black tar. The first three fractions failed to yield a pure picrate. From the fourth fraction a crude red picrate (200 mg.) was obtained, m. p. 95°, which after six crystallisations from methyl alcohol furnished 8 mg. of long needles of constant m. p. 121—122° (Found: C, 60·10; H, 5·47; N, 9·35. Calc. for $C_{16}H_{20}.C_6H_3O_7N_3$: C, 59·85; H, 5·25; N, 9·52%). From the mother liquors of the fourth fraction a small amount of impure cadalene picrate, m. p. 110—111°, was isolated which on being mixed with an authentic specimen softened at 100° and melted at 109—112°. The fifth fraction yielded the impure picrate of 1 : 6 : 7-trimethyl-4-*iso*propylnaphthalene, m. p. 117—118°, undepressed by a pure specimen obtained from the fourth fraction.

From the alkaline washings of the dehydrogenation product a crude ***naphthol*** was obtained on acidification and purified by sublimation at 100°/0·01 mm.; yield 30 mg. The product recrystallised from methyl alcohol as woolly needles, m. p. 116° (Found: C, 83·54, 83·58; H, 8·50, 8·66. $C_{15}H_{18}O$ requires C, 84·05; H, 8·46%). The dark red picrate separated from methyl alcohol in short needles, m. p. 139°, and the bright red trinitrobenzoate similarly in long needles, m. p. 139—140°.

The analyses are by Drs. Weiler and Strauss, Oxford.

We are indebted to the Chemical Society and the Australian and New Zealand Association for the Advancement of Science for grants, and to Dr. L. M. Cooke for Monel metal gauze used in the fractionating column. One of us (W. I. T.) is indebted for a Duffus Lubecki Scholarship.

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246. *Some Derivatives of* D-*Galacturonic Acid.*

By J. K. N. Jones and M. Stacey.

The synthesis is described of some derivatives of D-galacturonic acid, in particular 2-*methyl* α-*methyl*-D-*galacturonoside methyl ester*. This compound was oxidised to 2-*methyl galactosaccharic acid* (2-methyl mucic acid) a useful reference compound, while under stronger oxidising conditions some demethylation occurred with formation of galactosaccharic acid (mucic acid).

In addition to its widespread occurrence in plant gums and pectins, D-galacturonic acid forms a constituent of certain bacterial polysaccharides, *e.g.*, the Type I *pneumococcus* specific polysaccharide (Heidelberger, Goebel, and Avery, *J. Exp. Med.*, 1925, **42**, 701), and the polysaccharide of *Coccidioides immitis* (Hassid, Baker, and McCready, *J. Biol. Chem.*, 1943, **149**, 303).

It was necessary to synthesise partly methylated derivatives of D-galacturonic acid to serve as reference compounds in determination of bacterial polysaccharide structure. D-Galacturonic acid, obtained both by synthesis from D-galactose (Stacey, *J.*, 1939, 1529) and from citrus pectin by enzymic degradation, was converted into α-methyl-D-galacturonoside methyl ester [which has the pyranose structure (Levene and Kreider, *J. Biol. Chem.*, 1937, **120**, 597)] by boiling it with 1% methanolic hydrogen chloride for 8 hours. Treatment of this ester for 15 hours with acetone containing either 0·4% hydrochloric acid or anhydrous copper sulphate with a trace of concentrated sulphuric acid converted it into 3 : 4-*monoacetone* α-*methyl*-D-*galacturonoside methyl ester* (m. p. 107°; *monohydrate*, m. p. 70°).

This product was transformed on methylation with silver oxide and methyl iodide into the syrupy 2-methyl derivative. On being kept in a moist atmosphere the syrup crystallised in the form of its *monohydrate*. Removal of the acetone groups gave syrupy 2-*methyl* α-*methyl*-D-*galacturonoside methyl ester* (*amide*, m. p. 174°) which on being oxidised with nitric acid under moderate conditions gave 2-*methyl galactosaccharic acid*, a liquid (*amide*, m. p. 200°). Under more drastic oxidation conditions with nitric acid there was observed an unusual case of demethylation with production of free galactosaccharic acid in fairly good yield; cf. Anderson and Otis (*J. Amer. Chem. Soc.*, 1930, **52**, 4462), who effected the removal of non-glycosidic methyl residues from a mesquite gum by means of 72% sulphuric acid.

Experimental.

D-*Galacturonic Acid*.—This was prepared both from citrus pectin by the action of the enzyme, "Pectinol IOM," and from D-galactose by the synthetic method of Stacey (*loc. cit.*).

α-*Methyl*-D-*galacturonoside Methyl Ester*.—D-Galacturonic acid (5 g.) was boiled for 8 hours with 1% methanolic hydrogen chloride. The solution, neutralised with lead carbonate, was filtered and evaporated under diminished pressure to a syrup which rapidly crystallised. When recrystallised from methyl alcohol–acetone the substance had m. p. 147°, yield 50%, $[\alpha]_D^{20°}$ +128° (*c*, 1·0 in water); cf. Morell and Link (*J. Biol. Chem.*, 1933, **100**, 385).

3 : 4-*Monoacetone* α-*Methyl*-D-*galacturonoside Methyl Ester*.—(*a*) α-Methyl-D-galacturonoside methyl ester (1·2 g.) was shaken with acetone (50 c.c.) containing hydrogen chloride (0·2 g.) for 15 hours. The clear solution was poured into aqueous sodium hydrogen carbonate and the 3 : 4-monoacetone derivative extracted with chloroform. The extracts were dried ($MgSO_4$), and the filtered solution was evaporated in a vacuum. The *compound* (1·1 g.) had m. p. 107° (Found: C, 50·1; H, 6·8; OMe, 23·4. $C_{11}H_{18}O_7$ requires C, 50·4; H, 6·9; OMe, 23·6%).

(*b*) α-Methyl-D-galacturonoside methyl ester (5 g.) was shaken for 12 hours in acetone (200 c.c.) containing anhydrous copper sulphate (5 g.) and concentrated sulphuric acid (0·5 g.). The acid was neutralised with copper carbonate, and the filtered solution on evaporation yielded a crystalline product. When recrystallised from acetone–ligroin the product (4·5 g.) formed large prisms, m. p. 74°. On being heated or on being kept in a vacuum desiccator the crystals lost one molecule of water giving a product in the form of a fine white powder, m. p. 107°, $[\alpha]_D^{20°}$ +118° (*c*, 1·0 in water) (Found: C, 50·0; H, 6·9; OMe, 23·6%).

3 : 4-*Monoacetone* 2-*Methyl* α-*Methyl*-D-*galacturonoside Methyl Ester*.—The above monoacetone compound (3·0 g.) was dried and methylated thrice with silver oxide and methyl iodide, giving the *ester* as a syrup (3·0 g.), b. p. 124° (bath temp.)/0·3 mm., $n_D^{20°}$ 1·4210 (Found: OMe, 33·5. $C_{12}H_{20}O_7$ requires OMe, 33·7%). On exposure to a moist atmosphere the syrup slowly crystallised. When recrystallised from ethyl alcohol–ligroin the *monohydrate* had m. p. 38°, $[\alpha]_D^{20°}$ +116° (*c*, 1·1 in water) (Found: C, 49·2; H, 7·5; OMe, 32·4. $C_{12}H_{20}O_7,H_2O$ requires C, 49·1; H, 7·6; OMe, 31·6%).

2-*Methyl* α-*Methyl*-D-*galacturonoside Methyl Ester*.—A sample of the above compound (0·33 g.) was hydrolysed with boiling 33% acetic acid which converted it into a syrupy mixture of 2-methyl α-methyl-D-glacturonic acid and its methyl ester (Found: OMe, 35·7. Calc. for $C_8H_{14}O_7$: OMe, 27·7. Calc. for $C_9H_{16}O_7$: OMe, 39·5%). The syrup was dissolved in methyl alcohol and esterified by the addition of excess of diazomethane. After 2 hours the solvent was removed under reduced pressure and the residual syrup distilled; b. p. 190° (bath temp.)/0·3 mm., $n_D^{21°}$ 1·4732, $[\alpha]_D^{20°}$ +80° (*c*, 1·1 in water) (Found: OMe, 37·5. $C_9H_{16}O_7$ requires OMe, 39·5%). The *ester* was converted in the usual way into the *amide* which slowly crystallised; m. p. 174°, $[\alpha]_D^{18°}$ +55° (*c*, 0·05 in alcohol) (after recrystallisation from absolute ethanol–ether) (Found: N, 6·3; OMe, 27·5. $C_8H_{15}O_6N$ requires N, 6·3; OMe, 28·1%).

Oxidation of 2-Methyl 3 : 4-*Monoacetone* α-*Methyl-*D-*galacturonoside Methyl Ester.*—(*a*) A sample of the syrupy monoacetone compound (1·3 g.) was oxidised by treating it at 100° for 35 minutes with nitric acid (*d* 1·3). There was a copious deposit of crystalline material (0·5 g.) which was difficult to recrystallise. It had m. p. 219° (decomp.) alone or in admixture with galactosaccharic acid.

From the mother liquor there was obtained a small amount of oxalic acid and a syrup (0·5 g.) which was a mixture of ill-defined products.

(*b*) A further carefully redistilled fraction of the monoacetone compound (0·6 g.) was hydrolysed and the products were oxidised by heating them at 80° for 15 minutes with nitric acid (*d* 1·3). On being kept overnight the solution deposited only a trace of galactosaccharic acid. The nitric acid was distilled off with water and the syrupy product converted to the methyl ester (0·8 g.) which was distilled in a high vacuum; b. p. 160—162° (bath temp.)/0·07 mm., $[\alpha]_D^{20°}$ −19° (*c*, 0·27 in water), yield 0·5 g. The ester was converted into an *amide* which crystallised from water in the form of long needles, m. p. 200°, and gave a positive Weerman reaction (Found: C, 38·0; H, 6·5; N, 12·3; OMe, 14·4. $C_7H_{14}O_6N_2$ requires C, 37·8; H, 6·3; N, 12·6; OMe, 14·2%).

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247. *Synthesis of Some Derivatives of* D- *and* L-*Arabinose.*

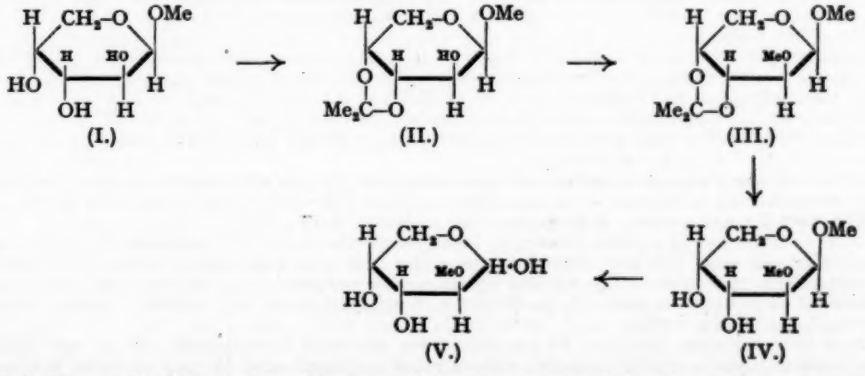
By J. K. N. JONES, P. W. KENT, and M. STACEY.

D-Arabinose has been converted into *2-methyl* D-*arabinose via* 3 : 4-*monoacetone* β-*methyl-*D-*arabopyranoside* and its 2-methyl derivative. Crystalline 2-p-*toluenesulphonyl* 3 : 4-*monoacetone* β-*methyl-*D-*arabopyranoside* has also been isolated together with the crystalline p-*toluenesulphonylhydrazone* of *2-methyl* D-*arabinose*. Analogous compounds, as well as the crystalline anilide of *2-methyl monoacetone* L-*arabinose*, have been obtained from L-arabinose.

THE identification of D-arabofuranose as a constituent sugar of the polysaccharides of *M. tuberculosis* (Haworth, Stacey, and Kent, *Abs. Amer. Chem. Soc.*, Chicago Meeting, 1946, 5 R.) is of considerable interest. Although the L-isomer has been found extensively in natural polysaccharides such as the plant gums, reports of the occurrence of D-arabinose in natural compounds are comparatively rare. Its presence in barbaloin has been claimed by Leger (*Bull. Soc. chim.*, 1910, **7**, 800) and it has been found in some animal secretions (Neuberg and Wohlgemuth, *Z. physiol. Chem.*, 1902, **35**, 31).

The wide occurrence of L-arabinose has led to the formation and study of many of its derivatives whereas the reactions and compounds of D-arabinose are incompletely known. With a view to obtaining reference compounds and to the chemical synthesis of biologically important pentose-related substances, *e.g.*, 2-deoxyribose compounds, a number of derivatives of D-arabinose were synthesised. The present paper describes these and also some derivatives of L-arabinose required for similar purposes.

D-Arabinose obtained from calcium gluconate by essentially the method of Hockett and Hudson (*J. Amer. Chem. Soc.*, 1934, **56**, 1562) was converted into crystalline β-methyl-D-arabopyranoside (I). When this compound was treated with acetone in the presence of a suitable dehydrating agent, it gave a syrupy monoacetone derivative which was shown to be 3 : 4-monoacetone β-methyl-D-arabopyranoside (II) as follows. On its being methylated with



methyl iodide and silver oxide there was formed a crystalline monomethyl monoacetone β-methyl-D-arabopyranoside (III) (m. p. 45°) which, on hydrolysis with methanolic hydrogen

chloride, afforded the 2-methyl β-methyl-D-arabopyranoside (IV) of von Schmidt and Simon (*J. pr. Chem.*, 1939, **152**, 190). This compound underwent further hydrolysis with aqueous acid giving 2-methyl D-arabinose (V) which was converted into a crystalline *p*-toluenesulphonylhydrazone having properties identical with those of the β-methyl-D-arabinose *p*-toluenesulphonylhydrazone obtained by von Schmidt and Simon (*loc. cit.*) by the degradation of 3-methyl D-glucose.

From the monoacetone glycoside (II) there were obtained the crystalline 2-*p*-toluenesulphonyl and 2-methanesulphonyl derivatives (m. p. 134° and 135° respectively), which could not be converted directly into the 2-iodo-compound.

In the presence of acetone and excess of concentrated sulphuric acid, β-methyl-D-arabopyranoside and monoacetone β-methyl-D-arabopyranoside, lost their glycosidic groups and were converted into diacetone D-arabinose which had properties analogous to those of the diacetone L-arabinose synthesised by Svanberg and Bergman (*Chem. Zentr.*, 1924, i, 1021).

It has been reported (Ohle and Berend, *Ber.*, 1927, **60**, 810) that treatment of L-arabinose with acetone in the presence of anhydrous cupric sulphate gave a monoacetone derivative which reduced Fehling's solution. An analogous *monoacetone* derivative has now been prepared from D-arabinose, and although the structure of this has not been fully investigated it is likely that the *iso*propylidene group engages the 3 : 4-positions. Thus on further treatment with acetone containing 2% sulphuric acid the monoacetone compound was converted into a non-reducing diacetone D-arabinose. This was identical with a diacetone D-arabinose prepared by the action of acetone containing 3% sulphuric acid upon either β-methyl-D-arabinoside or monoacetone β-methyl-D-arabopyranoside in which it is known that the acetone group engaged the 3 : 4-positions.

In the L-series, β-methyl-L-arabopyranoside was converted into 3 : 4-*monoacetone* β-*methyl*-L-*arabopyranoside*, from which a crystalline 2-*toluenesulphonyl* derivative (m. p. 134°) was obtained. Methylation of the monoacetone glycoside afforded 2-*methyl* 3 : 4-*monoacetone* β-*methyl*-L-*arabopyranoside*. In this compound scission of the acetone group was effected by treatment with acetic acid, and the product, 2-*methyl* β-*methyl*-L-*arabopyranoside*, was hydrolysed with dilute sulphuric acid giving 2-*methyl* L-*arabinose* from which a crystalline *phenylhydrazone* was isolated.

Treatment of 2-methyl L-arabinose with acetone in the presence of a dehydrating agent yielded a crystalline 2-*methyl monoacetone* L-*arabinose* which was reducing to Fehling's solution and, on being boiled with ethanolic aniline, gave a readily crystallised *anilide*.

Experimental.

D-*Arabinose from Calcium* D-*Gluconate*.—The method employed was a modification of that described by Hockett and Hudson (*J. Amer. Chem. Soc.*, 1934, **56**, 1632). A solution of ferric acetate, prepared by addition of 21 g. of ferric sulphate in 60 c.c. of water to 10·5 g. of barium acetate in 60 c.c. of water, was mixed with calcium D-gluconate (200 g. in 2 l. of water), and the resulting solution heated to boiling. After filtration, the solution was warmed to 60° and 120 c.c. of 30% hydrogen peroxide in 1 l. of water were slowly added. After 2 hours, a further 120 c.c. of 30% hydrogen peroxide was added to the dark solution (at 60°). After 2 hours the solution was filtered and evaporated to 200 c.c. under diminished pressure. To the resulting syrup methanol (1600 c.c.) and ether (800 c.c.) were added. The precipitate formed was separated and the filtrate concentrated further to a thick syrup, which readily crystallised on standing at 0°. Yield of recrystallised D-arabinose, 51 g.; m. p. 155°; $[\alpha]_D^{18°}$ − 105° (*c*, 1·5 in water).

D-Arabinose (2 g.) was shaken with dry acetone (1 l.), anhydrous cupric sulphate (80 g.), and barium carbonate (10 g.) for 8 days at room temperature. The filtered solution was evaporated to dryness and the resulting syrup recrystallised from ether (0·2 g.); m. p. 78°; $[\alpha]_D^{19°}$ − 111° (*c*, 1·1 in water, no mutarotation) (cf. monoacetone L-arabinose, Ohle and Berend, *loc. cit.*; m. p. 76—77°; $[\alpha]_D$ + 128°). Treatment of this product with acetone and concentrated sulphuric acid yielded diacetone D-arabinose; m. p. 40—41° $[\alpha]_D^{19°}$ −4° (*c*, 1·1 in water).

3 : 4-*Monoacetone* β-*Methyl*-D-*arabinoside*.—D-Arabinose (25 g.) was converted into the glycoside by being refluxed with methanolic hydrogen chloride (1%; 500 c.c.) for 10 hours. The β-form readily crystallised from a small amount of methanol; m. p. 168°. Yield, 12 g.

β-Methyl D-arabinose (2 g.) was shaken at room temperature with dry acetone (100 c.c.) and concentrated sulphuric acid (1·0 c.c.) for 72 hours. The acid was neutralised (litmus) by addition of anhydrous sodium carbonate. The filtered solution was evaporated to dryness, and the remaining syrup distilled in a high vacuum; b. p. 90° (vap. temp.)/0·3 mm.; $n_D^{19°}$ 1·4600 (Found: OMe, 9·2. Calc. for $C_9H_{16}O_5$: OMe, 8·9%).

β-Methyl-D-arabinoside (10 g.) or 3 : 4-monoacetone β-methyl-D-arabinoside (10 g.) was shaken for 24 hours with dry acetone (300 c.c.) and concentrated sulphuric acid (5 c.c.) at room temperature. After neutralisation with sodium carbonate the filtered solution was evaporated to dryness and distilled in a high vacuum. The distillate rapidly crystallised from ligroin; m. p. 41°; OMe content, nil (m. p. 41·5—43° for diacetone L-arabinose; Svanberg and Bergman, *loc. cit.*).

2-p-*Toluenesulphonyl* 3 : 4-*Monoacetone* β-*Methyl*-D-*arabinoside*.—3 : 4-Monoacetone β-methyl-D-arabinoside (0·2 g.) was dissolved in dry pyridine (7 c.c.) to which was added *p*-toluenesulphonyl chloride (0·8 g.). After 24 hours at room temperature the mixture was poured into water (200 c.c.), and the crude *product* which separated was recrystallised from alcohol (0·2 g.); m. p. 134° (Found: C, 53·3; H, 6·1; S, 9·3; OMe, 9·2. $C_{16}H_{22}O_7S$ requires C, 53·5; H, 6·15; S, 8·95; OMe, 8·65%).

2-*Methanesulphonyl* 3 : 4-*Monoacetone* β-*Methyl*-D-*arabinoside*.—3 : 4-Monoacetone β-methyl-D-arabinoside (0·3 g.) was dissolved in dry pyridine (10 c.c.) and treated with methanesulphonyl chloride (0·5 g.). After 48 hours the solution was poured into water (250 c.c.). No solid separated, and the aqueous solution was extracted several times with chloroform. The chloroform solution was washed with dilute hydrochloric acid and then with water and finally dried (Na_2CO_3). Evaporation of the resulting solution afforded a syrup which readily crystallised (0·2 g.) from alcohol; the *compound* had m. p. 135° (Found: OMe, 10·9. $C_{10}H_{18}O_7S$ requires OMe, 11·0%).

Attempted Formation of 2-*Iodo* 3 : 4-*Monoacetone* β-*Methyl*-D-*arabinoside*.—(i) 2-*p*-Toluenesulphonyl 3 : 4-monoacetone β-methyl-D-arabinoside (0·2 g.) was dissolved in dry acetone (20 c.c.) to which was added dry sodium iodide (2 g.). The mixture was heated at 110° for 12 hours in a sealed tube. The starting material (0·16 g.) was recovered unchanged.

(ii) 2-Methanesulphonyl 3 : 4-monoacetone β-methyl-D-arabinoside (0·5 g.) was heated with dry acetone (25 c.c.) and sodium iodide (2 g.) in a sealed tube at 110° or 130° for 48 hours. The starting material was recovered unchanged.

Methylation of 3 : 4-*Monoacetone* β-*Methyl*-D-*arabopyranoside*.—The monoacetone glycoside (0·7 g.) was heated for 6 hours with methyl iodide (5 c.c.) and silver oxide (1 g.). After 3 such methylations, the syrupy product was distilled; b. p. 136—137° (bath temp.)/2 mm. The distillate ($n_D^{16°}$ 1·4520) readily crystallised on standing, and after recrystallisation from acetone–ligroin the *compound* had m. p. 43°; $[\alpha]_D^{19°}$ − 145° (*c*, 1·8, in water) (Found: C, 55·1; H, 8·2; OMe, 28·2. $C_{10}H_{18}O_5$ requires C, 54·9; H, 8·3; OMe, 28·4%). Yield, 0·5 g.

Formation of 2-*Methyl* β-*Methyl*-D-*arabopyranoside*.—2-Methyl 3 : 4-monoacetone β-methyl-D-arabopyranoside (0·3 g.) was heated for 3 hours with methanolic hydrogen chloride (20 c.c.; 5%); $[\alpha]_D^{20°}$ − 130° → − 35°. The resulting solution was neutralised (litmus) with silver carbonate and the filtrate evaporated, giving a syrup, $n_D^{16°}$ 1·4602, which crystallised on standing (0·2 g.). After recrystallisation from methanol–ether the *compound* had m. p. 48° (Found: OMe, 31·6. $C_7H_{14}O_5,H_2O$ requires OMe, 31·6%).

2-*Methyl* D-*Arabinose*.—2-Methyl β-methyl-D-arabopyranoside (0·2 g.) was heated at 100° for 6 hours with sulphuric acid (N; 10 c.c.); $[\alpha]_D^{18°}$ − 96° → − 56°. The solution reduced Fehling's solution and was neutralised (phenolphthalein) with sodium hydroxide and evaporated, and the residue extracted with chloroform. On evaporation of the chloroform extract to dryness, 2-*methyl* D-*arabinose* was obtained as a reducing syrup (0·1 g.); $n_D^{17°}$ 1·4710 (Found: OMe, 18·6. $C_6H_{12}O_5$ requires OMe, 18·9%).

Treatment of this syrup with phenylhydrazine (3 drops), glacial acetic acid (4 drops), and water (2 c.c.) at room temperature for several hours afforded a crystalline *phenylhydrazone* which, after recrystallisation from aqueous ethanol, had m. p. 113° (Found: OMe, 12·2. $C_{13}H_{18}O_4N_2$ requires OMe, 12·2%).

Formation of 2-*Methyl* D-*Arabinose* p-*Toluenesulphonylhydrazone*.—2-Methyl D-arabinose (0·1 g.) was dissolved in absolute alcohol (8 c.c.), treated with *p*-toluenesulphonylhydrazine (Freudenberg and Blümmel, *Annalen*, 1924, **440**, 51) (0·1 g.), and the mixture heated under reflux for 1 hour. On removal of the solvent, the p-*toluenesulphonylhydrazone* separated, and after recrystallisation from aqueous alcohol had m. p. 143° (decomp.); $[\alpha]_D^{16°}$ − 17·0° (*c*, 0·8 in water) (initial value) (Found: OMe, 9·1. $C_{13}H_{20}O_6N_2S$ requires OMe, 9·4%).

3 : 4-*Monoacetone* β-*Methyl*-L-*arabinoside*.—(*a*) β-Methyl-L-arabopyranoside (2 g.) was shaken with acetone (250 c.c.) and anhydrous copper sulphate (10 g.) for 7 days. The solution was then filtered and the filtrate concentrated under diminished pressure to a syrup (2 g.), $n_D^{22°}$ 1·4642.

(*b*) (Cf. Robertson and Speedie, *J.*, 1934, 824.) The arabinoside (2 g.) was shaken with acetone (20 c.c.) containing hydrogen chloride (2 g.) for 48 hours. The clear solution was then poured into excess of dilute sodium hydroxide solution and the product extracted thrice with chloroform. The chloroform solution was then dried (Na_2CO_3), filtered, and concentrated under reduced pressure to a syrup (1·8 g.) which was distilled; the *compound* had b. p. 105° (bath temp.)/0·01 mm.; $n_D^{23°}$ 1·4628 (Found: C, 52·9; H, 8·1. $C_9H_{16}O_5$ requires C, 52·9; H, 7·9%)

The corresponding 2-p-*toluenesulphonyl* derivative was prepared by reaction of 3 : 4-monoacetone β-methyl-L-arabinoside (4·0 g.) with *p*-toluenesulphonyl chloride (4·5 g.; 1·1 ml.) in dry pyridine (25 c.c.) at 40°. The warm solution was diluted with water and cooled, and the product filtered off and dried. Yield, 4·5 g.; m. p. 134° (Found: C, 53·8; H, 5·6; OMe, 8·6. $C_{16}H_{22}O_7S$ requires C, 53·6; H, 6·2; OMe, 8·7%). Hydrolysis of this product with boiling 50% acetic acid gave 2-*p*-toluenesulphonyl β-methyl-L-arabinoside in low yield as deliquescent crystals of low melting point. The product was not further examined.

2-*Methyl* 3 : 4-*Monoacetone* β-*Methyl*-L-*arabopyranoside*.—3 : 4-Monoacetone β-methyl-L-arabopyranoside (2 g.) was methylated with silver oxide and methyl iodide and the product distilled under reduced pressure. The corresponding 2-*methyl ether* distilled at 100° (bath temp.)/0·01 mm.; $n_D^{20°}$ 1·4481 (Found: C, 54·9; H, 8·3; OMe, 28·4. $C_{10}H_{18}O_5$ requires C, 55·1; H, 8·2; OMe, 28·4%).

2-*Methyl* β-*Methyl*-L-*arabopyranoside*.—2-Methyl 3 : 4-monacetone β-methyl-L-arabopyranoside (1·86 g.) was boiled with water (20 c.c.) containing glacial acetic acid (5 c.c.) for 2 hours ($[\alpha]_D^{20°}$ +202° initial value, → + 186°). The solution was concentrated under reduced pressure to a syrup which was distilled in a vacuum; b. p. 130° (bath temp.)/0·01 mm.; $n_D^{21°}$ 1·4768. This *product* crystallised shortly after distillation; m. p. 59° (Found: C, 47·0; H, 8·2; OMe, 34·2. $C_7H_{14}O_5$ requires C, 47·2; H, 7·9; OMe, 34·8%). On recrystallisation from acetone–ether the arabinoside separated as the *monohydrate*, m. p. 47° (Found: C, 42·9; H, 7·7; OMe, 31·4. $C_7H_{14}O_5,H_2O$ requires C, 42·9; H, 8·2; OMe, 31·6%).

2-*Methyl* L-*Arabinose*.—β-Methyl 2-methyl-L-arabinoside (1·06 g.) was hydrolysed with boiling N-sulphuric acid (25 c.c.) for 4 hours; $[\alpha]_D^{20°}$ + 234° (initial value) → + 99° (constant value). The

cooled solution was neutralised with barium carbonate and filtered, and the filtrate evaporated under reduced pressure to a syrup which did not crystallise. With alcoholic phenylhydrazine crystalline *2-methyl* L-*arabinose phenylhydrazone* was obtained, m. p. 116° after recrystallisation from alcohol–ether–light petroleum (Found: C, 56·8; H, 7·8; N, 10·9; OMe, 12·4. $C_{12}H_{18}O_4N_2$ requires C, 56·7; H, 7·1; N, 11·0; OMe, 12·2%). No crystalline anilide could be isolated.

On shaking an acetone solution with anhydrous copper sulphate 2-methyl L-arabinose gave *2-methyl monoacetone* L-*arabinose* which, on evaporation of the filtered solution, was isolated as a crystalline reducing solid, m. p. 117°. It was purified by recrystallisation from acetone and sublimed in a vacuum (Found: C, 52·8; H, 7·8; OMe, 15·1. $C_9H_{16}O_5$ requires C, 52·9; H, 7·8; OMe, 15·2%).

On being heated with alcoholic aniline this product gave crystalline *2-methyl monoacetone* L-*arabinose anilide*, m. p. 143° after recrystallisation from ethyl alcohol (Found: C, 64·4; H, 7·4; N, 4·8; OMe, 11·0. $C_{15}H_{21}O_4N$ requires C, 64·6; H, 7·4; N, 5·0; OMe, 11·1%).

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248. *The Quantitative Separation of Methylated Sugars.*

By F. BROWN and J. K. N. JONES.

Two methods for the quantitative separation of fully methylated sugars from their partly methylated derivatives are described. The first is a standardised procedure for the quantitative chromatographic separation of methylated sugar glycosides on activated alumina by means of which quantities as small as 245 mg. of tetramethyl methylglucoside can be separated from a large excess of 2 : 3 : 6-trimethyl methyl-*d*-glucoside. In the second method the fully methylated sugar glycoside, which may weigh as little as 36 mg., can be recovered from admixture with a large excess of admixed partly methylated sugar glycosides by preferential extraction of the fully methylated derivative with light petroleum from water using two continuous extraction apparatuses, one fitted above the other.

DETAILED knowledge of structure in the carbohydrate group has been largely dependent upon the possibility of separating and identifying the various components of the mixture of methylated sugars obtained on hydrolysis of the methyl ethers of the materials under investigation. The quantitative aspect of this problem assumed special importance in the development of the chemical end group method applied by Haworth and Machemer (*J.*, 1932, 2270) in their determination of the chain length of cellulose. This involved the quantitative separation, by fractional distillation, of a very small amount of tetramethyl glucose from a larger amount of 2 : 3 : 6-trimethyl glucose, similar problems being met with in studies on starch and glycogen. Even in this comparatively simple case complications are encountered in the course of the fractional distillation of the mixture of methylated methylglucosides, and special methods had to be adopted in order to obtain accurate results (see Hirst and Young, *J.*, 1938, 1247; Averill and Peat, *ibid.*, p. 1244; Peat and Whetstone, *J.*, 1940, 276). In the course of attempts to overcome the difficulties inherent in the method of separation by distillation other procedures have been elaborated, including, for example, (*a*) phosphorylation of the partly methylated glycosides followed by extraction of the fully methylated glycoside from aqueous solution by organic solvents (Hess and Neumann, *Ber.*, 1937, **70**, 710; Leckzyik, *ibid.*, 1938, **71**, 829; Hess, Grigorescu, Steurer, and Forham, *Ber.*, 1940, **73**, 505), and (*b*) separation of the sugars on silica (Bell, *J.*, 1944, 473), or chromatographic separation of the glycosides on alumina (Jones, *J.*, 1944, 333).

An outline of the method of separation of methylated sugar glycosides on alumina has already been given (Jones, *loc. cit.*). We have now standardised this method and find it so sensitive that even the α- and β-methylglucosides of tetramethyl glucopyranose may be separated partially one from another. The recovery of the sugars by this procedure amounts to 93% of the fully methylated sugar, so that a small correction is necessary in order to obtain the exact amount of end-group present.

A further method, which we have developed quantitatively on the semi-micro scale, depends upon the fact that fully methylated sugars are much more readily extracted from water with light petroleum (b. p. 38—40°) than are partly methylated sugars. Tetramethyl methylglucoside has a partition coefficient of about 10 between chloroform and water whilst the partition coefficient found for 2 : 3 : 6-trimethyl methylglucoside is about 2 between chloroform and water (cf. the work of Macdonald, *J. Amer. Chem. Soc.*, 1935, **57**, 771, who determined the coefficient for the corresponding free sugars). We have found that the partition coefficient of fully methylated glucose between light petroleum (b. p. 38—40°) and water is about 0·1 whilst the correspond-

ing figure for trimethyl methylglucoside is $<0{\cdot}01$. The ratio between these last two figures is such that we were able to develop a method for the separation of the sugar derivatives by a continuous extraction process.

In carrying out the separation two continuous extractors are fitted, one above the other. In the top apparatus is placed the mixture of glycosides dissolved in water or sodium hydroxide solution, whilst the bottom apparatus initially contains water only. The apparatus is connected to a reservoir flask containing boiling light petroleum (b. p. 38—40°). The vapours are condensed and drop through the top solution and extract a mixture of sugars, mainly the fully methylated α- and β-glycosides; the extracts are then washed by passing through the water in the lower apparatus and finally return to the reservoir. This extraction is interrupted at intervals, solvent evaporated, the residual syrup weighed, and the refractive index determined. When a refractive index, combined with optical rotatory determination, shows the extract to be free from the fully methylated derivative (Hirst and Young, *loc. cit.*), the previous extracts are combined and dissolved in water, and the whole process is repeated in a similar apparatus. Eventually, following this technique, fractions consisting of fully methylated glycosides free from partly methylated sugars are obtained. In trial experiments the recovery of fully methylated sugar glycosides was of the order of 98—102%. By the use of this method the quantitative separation of the methylglucosides of 2 : 3 : 4 : 6-tetramethyl *d*-glucose and 2 : 3 : 6-trimethyl *d*-glucose (1 : 1 mixtures), and of 2 : 3 : 4 : 6-tetramethyl *d*-galactose and 2 : 3 : 6-trimethyl *d*-glucose (1 : 1 mixtures) has been achieved. This method has also been applied successfully to the quantitative separation of one part of tetramethyl methylglucoside (36 mg.) from 24 parts of partly methylated methylglucosides (865 mg.), and can be used with reasonable accuracy for still lower concentrations of the fully methylated sugar. These methods can therefore be applied to the determination of the size of the repeating unit of methylated polysaccharides. Since the partition method is applicable also to the quantitative separation of fully methylated pentose sugars from partially methylated pentose and hexose sugars, it can be used for the quantitative determination of the sugars formed on methanolysis of the complex methyl ethers of gums and mucilages; as an example of its utility the quantitative separation of the methylglycosides produced on hydrolysis of methylated peanut araban is described. The results obtained are in full agreement with those obtained by using the distillation procedure (Hirst and Jones, in the press).

Experimental difficulties may arise if the methylated polysaccharide is not rigorously purified before methanolysis, since any impurities present in it which are soluble in light petroleum will contaminate the fully methylated sugar finally obtained. In the event of a coloured and impure fraction of fully methylated sugar being isolated it may be purified by distillation in an apparaus of the type described by Ellis (*Chem. and Ind.*, 1934, 77). The loss during the final distillation is less than 1 mg. on quantities of the order of 40 to 100 mg. of tetramethyl methyl-*d*-glucoside.

Experimental.

As a result of many experiments with various solvents and weights of alumina the following technique was found to be the most satisfactory for the separation of tetramethyl α- and β-methyl-*d*-glucoside from a mixture of 2 : 3 : 4 : 6-tetramethyl methyl-*d*-glucoside and 2 : 3 : 6-trimethyl methyl-*d*-glucoside.

A solution of 2 : 3 : 4 : 6-tetramethyl α-methyl- (530 mg.) and β-methyl- (515 mg.) *d*-glucoside and 2 : 3 : 6-trimethyl methyl-*d*-glucoside (1·02 g., prepared from pure 2 : 3 : 6-trimethyl *d*-glucose) in light petroleum (b. p. 60—80°; washed with sulphuric acid and sodium hydroxide solution and distilled) was passed through a column of alumina (from the British Aluminium Co., Burntisland, Scotland, activated at 360° for 4 hours; 350 g., length 18 ins., cross section 1¼ ins.), and the column developed with chloroform [dried ($CaCl_2$) and distilled]. The eluate was collected in fractions (100 c.c.) each of which was tested for the presence of sugars by the Molisch test after withdrawing a sample (5 c.c.) and removing the solvent by evaporation. After the passage of chloroform (1100 c.c.), fractions of sugar were isolated having the following properties, all rotations being measured in chloroform solution: (1) 50 mg., $n_D^{16°}$ 1·4440, $[\alpha]_D^{16°}$ +75°; (2) 60 mg., $n_D^{16°}$ 1·4436, $[\alpha]_D^{16°}$ +110°; (3) 125 mg., $n_D^{16°}$ 1·4442, $[\alpha]_D^{16°}$ +130°; (4) 90 mg., $n_D^{16°}$ 1·4437, $[\alpha]_D^{16°}$ +83°; (5) 70 mg., $n_D^{16°}$ 1·4436, $[\alpha]_D^{16°}$ +68°; (6) 105 mg., $n_D^{16°}$ 1·4420, $[\alpha]_D^{16°}$ +20°; (7) 440 mg., $n_D^{16°}$ 1·4414 (superfused), $[\alpha]_D^{16°}$ −25°. The syrup from this fraction crystallised; m. p. 37°. Total yield, 940 mg. (92% recovery). The next fractions gave a weak positive Molisch test but left no weighable residue of sugar on evaporation. The trimethyl methyl-*d*-glucoside was eluted with methyl alcohol. Yield, 1·0 g. Since the yield of fully methylated sugar which would be isolated from a partly methylated starch of weight 5 g. (an amount convenient to handle in methylation work) is about 240 mg., tetramethyl methylglucoside (245 mg., $n_D^{16°}$ 1·4440) and trimethyl methylglucoside (382 mg., $n_D^{16°}$ 1·4572) were separated. The sugars, dissolved in light petroleum (b. p. 40—60°, 50 c.c.), were passed through a column of activated alumina (18 ins. × 1¼ ins.). The alumina was then eluted with alcohol-free, dry chloroform and the following fractions of sugars isolated on concentration of 100 c.c. portions of the chloroform eluate: Fraction A (28 mg.), $n_D^{16°}$ 1·4462; Fraction B (49 mg.), $n_D^{16°}$ 1·4460; Fraction C (51 mg.), $n_D^{16°}$ 1·4449; Fraction D (24 mg.), $n_D^{16°}$ 1·4440; Fraction E (54 mg.), $n_D^{16°}$ 1·4420; Fraction F (20 mg.), $n_D^{16°}$ 1·4415. This last fraction crystallised; m. p. of solid, 37°. Two further

fractions contained a negligible amount of sugar (<1 mg.)—thereafter trimethyl methylglucoside was eluted. This yield of sugars (Fractions A to F, 226 mg.) corresponds to a yield of 93%.

Since the yield of 2 : 3 : 4 : 6-tetramethyl methyl-*d*-glucoside was 92%, a correction is necessary when applying this method to the determination of the repeating unit of methylated starch or glycogen. The technique described above is applied to the separation of approximately equal parts of tetramethyl and trimethyl methyl-*d*-glucosides. To approximate to these conditions when carrying out a determination of the repeating unit of a polysaccharide it is necessary to carry out a preliminary enrichment of the "tetra" fraction present in the hydrolysis products from the methylated polysaccharides. This is carried out by the following general procedure. The methylated polysaccharide is hydrolysed by boiling with methanolic hydrogen chloride. After neutralisation of the solution, with silver carbonate, N-sodium hydroxide (slight excess), or diazomethane, and filtration if necessary, solvent is removed at 760 mm. on the water-bath and finally in a vacuum at 25°, and the residual syrup dissolved in water (*ca.* 50 c.c.) and extracted continuously with redistilled sulphur-free light petroleum in an all-glass apparatus for about 4 hours. This procedure usually removes all the fully methylated sugar from the aqueous solvents along with about an equal weight of trimethyl methylglucoside. To guard against incomplete extraction, the water solution is again extracted with light petroleum (b. p. 38—40°) for about 4 hours, and the extracts are added to the first extract. If the sodium hydroxide neutralisation technique is used, contamination of the fraction rich in fully methylated sugar with methyl lævulate is avoided. These extracts are then combined and concentrated, and the product is weighed and subsequently separated on the column as described above.

Quantitative Separation of Fully Methylated Sugars from Partly Methylated Sugars by Partition between Water and Light Petroleum (b. p. 38—40°).—The mixture of methylated methylglucosides is dissolved in dilute sodium hydroxide solution (to remove traces of acids and esters) and extracted continuously in an apparatus consisting of two all-glass continuous extraction vessels ("Quickfit" and Quartz/EX8/23) in series. The solution of sugars (40 c.c.) is placed in the top apparatus; the second extractor contains water (75 c.c.) which serves the purpose of washing the light petroleum extracts.

In a trial experiment fully methylated glucose ($n_D^{16°}$ 1·4434; 257 mg.) and trimethyl methylglucoside ($n_D^{16°}$ 1·4572; 223 mg.) were dissolved in water (40 c.c.) and extracted in the apparatus for 2¾ hours. Concentration of the extract gave a syrup (235 mg.; $n_D^{16°}$ 1·4434; $[\alpha]_D^{20°}$ +53°, in water). Further extraction for two hours gave a syrup (20 mg.; $n_D^{16°}$ 1·4430; $[\alpha]_D^{20°}$ +40°, in water). Two further extracts of 2 hours each gave products (9 mg. and 12 mg.) which were trimethyl methylglucoside. Recovery is therefore 255 mg. or 99%.

In a second experiment tetramethyl methylglucoside (126 mg.; $n_D^{16°}$ 1·4437) and trimethyl methylglucoside (129 mg.; $n_D^{16°}$ 1·4572) were dissolved in water (50 c.c.) and extracted as before for 2½ hours. Concentration of the extract left a residual syrup (107 mg.; $n_D^{16°}$ 1·4431; $[\alpha]_D^{20°}$ +38°). Further extraction for 2 hours gave a syrup (23 mg.; $n_D^{16°}$ 1·4423; $[\alpha]_D^{20°}$ +14°). Continuation of the extraction (2 periods of 2 hours) gave on concentration a very small yield of syrup (1—2 mg.). Recovery of fully methylated glucose, 102%.

In the above two experiments the ratio of tetramethyl to trimethyl methylglucoside is about 1 : 1. With most polysaccharides, *e.g.*, starches and celluloses, the proportion of end group is much less than this, and further experiments were carried out to test the accuracy of this method when applied to mixtures containing one part of tetramethyl methylglucoside to 19—34 parts of trimethyl methylglucoside. Fully methylated glucose (140 mg.; $n_D^{16°}$ 1·4438) and trimethyl methylglucoside (2577 mg.; $n_D^{16°}$ 1·4574) were dissolved in water (50 c.c.) and extracted for 5 hours. Concentration of the extract left a syrup (C) (347 mg.; $n_D^{16°}$ 1·4510). Further extraction with light petroleum gave a syrup (93 mg.; $n_D^{16°}$ 1·4550) which contained no fully methylated glucose since on extraction in the same way for 5 hours it yielded trimethyl *d*-methylglucoside (7 mg.) only. Accordingly the extract (C) (347 mg.) was dissolved in water (50 c.c.) and extracted once again for 5 hours. Yield of syrup, 138 mg.; $n_D^{16°}$ 1·4434; $[\alpha]_D^{20°}$ +60° (in water). Further extraction for two hours gave the partly methylated glucose (16 mg.), $n_D^{16°}$ 1·4562. Recovery of fully methylated glucose is therefore 138 mg. (98·5%).

In another experiment a mixture of tetramethyl (53 mg.; $n_D^{16°}$ 1·4438) and 2 : 3 : 6-trimethyl methyl-*d*-glucoside (1715 mg.; $n_D^{16°}$ 1·4574) and 2 : 3-dimethyl methylglucoside (157 mg.,; m.p. 79°) were put through this double procedure which resulted in a recovery of 98% of the fully methylated sugar (52 mg.; $n_D^{16°}$ 1·4441; $[\alpha]_D^{20°}$ +80°).

In a further experiment a mixture of tetramethyl methylglucoside (36 mg.; $n_D^{16°}$ 1·4440), 2 : 3 : 6-trimethyl methylglucoside (865 mg.; $n_D^{16°}$ 1·4582), and 2 : 3-dimethyl methylglucoside (26 mg.; m. p. 79°) was extracted in the same way and gave a recovery of the fully methylated sugar of 100% (36 mg.; $n_D^{16°}$ 1·4441; $[\alpha]_D^{20°}$ +80° in water).

Separation of Tetramethyl Methylgalactoside and 2 : 3 : 6-Trimethyl Methylglucoside.—Heptamethyl methyl-lactoside (199 mg.; m. p. 77—79°) was dissolved in boiling methanolic hydrogen chloride (25 c.c.; 1%) and hydrolysed by boiling the solution for 8 hours. The solution was then neutralised with N-sodium hydroxide and concentrated in a vacuum to a syrup which was dissolved in water (50 c.c.) and extracted continuously with light petroleum (b. p. 38—40°) in the standard apparatus. Continuous extraction of the aqueous solution for 9 hours gave tetramethyl methylgalactoside [105 mg. (96%); $n_D^{16°}$ 1·4492] on concentration of the extracts. Further extraction for 3 hours gave, on removal of the solvent, < 3 mg. of syrup. The syrup (105 mg.) was hydrolysed with boiling N-hydochloric acid, and the syrupy 2 : 3 : 4 : 6-tetramethyl *d*-galactose isolated in the usual manner and identified by conversion into the corresponding crystalline anilide, m. p. and mixed m. p. with an authentic specimen, 190°. The aqueous solutions remaining in the apparatus were then combined and extracted continuously with chloroform. Removal of the solvent left 2 : 3 : 6-trimethyl methylglucoside [102 mg. (98%); $n_D^{16°}$ 1·4574], identified after hydrolysis with boiling N-hydrochloric acid as 2 : 3 : 6-trimethyl *d*-glucose.

Separation of the Hydrolysis Products of Methylated Peanut Araban.—(*a*) Methylated peanut araban (4·4 g.) was boiled with methanolic hydrogen chloride (1%; 100 c.c.) during 7 hours. The cooled solution was neutralised with silver carbonate and filtered. The filtrate on concentration gave a mixture of glycosides (5·2 g.) which was fractionated. A portion of this syrupy product (1·519 g.) was dissolved in water

(50 c.c.) and extracted continuously in a double extractor with purified light petroleum (b. p. 38—40°). The following fractions were obtained: Fraction 1 (0·498 g.), $n_D^{23°}$ 1·4380; Fraction 2 (0·039 g.), n_D^{20} 1·4439; Fraction 3 (0·53 g.), $n_D^{19°}$ 1·4510. Fractions 1 and 2 contained 0·517 g. of trimethyl methyl-*l*-arabinoside corresponding to a yield of 32% (calculated on the weight of glycosides) (Found by the distillation method: 32·2%).

(*b*) A further portion of the methanolysis product (1·31 g.) of methylated peanut araban was dissolved in water (50 c.c.) and extracted continuously in a double extractor as described above. The following fractions were isolated: 2 : 3 : 5-Trimethyl methyl-*l*-arabinoside (0·42 g.), $n_D^{16°}$ 1·4390 (Found: OMe, 59·7. Calc. for $C_9H_{18}O_5$: OMe, 60·2%); 2 : 3-dimethyl methyl-*l*-arabinoside (0·40 g.), $n_D^{16°}$ 1·4530 (Found: OMe, 48·2. Calc. for $C_8H_{16}O_5$; OMe, 48·4%). The residual aqueous solution on concentration gave 2-methyl methyl-*l*-arabinoside (0·46 g.), $n_D^{18°}$ 1·4749 (Found: OMe, 37·2. Calc. for $C_7H_{14}O_5$: OMe, 34·8%). Total recovery of sugars, 98%. These figures indicate that trimethyl, dimethyl, and monomethyl methyl-*l*-arabinoside were present after methanolysis in equimolecular proportions.

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249. *Qualitative Semimicro-analysis with Reference to Noyes and Bray's System: Partial Analysis of the Combined Nickel, Zirconium, and Rare-earth Groups.*

By CHRISTINA C. MILLER.

A scheme of analysis is presented for the detection and approximate determination of 0·25—50 mg. of manganese, cobalt, or nickel, 0·25—10 mg. of titanium, zirconium, indium, or scandium, and a small amount of zinc (minimum 0·25 mg.) in solutions containing a maximum of 50 mg. referred to the metals. These include all the more important elements present in the combined nickel, zirconium, and rare-earth groups of Noyes and Bray's scheme. The maximum amount of any one rare-earth group metal is 10 mg. In separate portions of the solution, manganese, cobalt, nickel, titanium, and zirconium are detected, respectively, by means of potassium periodate, ammonium thiocyanate and extraction with butyl acetate, dimethylglyoxime, chromotropic acid, and *p*-hydroxyphenylarsonic acid. In a sixth portion zinc is separated from cobalt and more than 1 mg. of nickel, and tested for with copper sulphate and ammonium mercury thiocyanate. Finally, in a seventh portion indium and scandium are isolated. Indium is precipitated as indium sulphide and confirmed with alizarin, and scandium detected by means of alizarin-S or morin.

SCHEMES for the analysis on a semimicro-scale of seven groups of Noyes and Bray's system ("A System of Qualitative Analysis for the Rare Elements," 1927) have already been reported by Miller and Lowe (*J.*, 1940, 1258, 1263) and Miller (*J.*, 1941, 72, 786; 1943, 72). This paper describes the further application of semimicro-analytical methods to the detection of manganese, cobalt, nickel, zinc, titanium, zirconium, indium, and scandium in a group containing all the more important metals associated with the nickel, zirconium, and rare-earth groups of Noyes and Bray's scheme.

After removing metals precipitable by hydrogen sulphide in acid solution, Noyes and Bray precipitate those of the ammonium sulphide group in two separate operations. From one precipitate iron, gallium, and components of the aluminium group are eliminated, leaving indium, zirconium, and titanium (zirconium group), some rare-earth group metals, and traces of cobalt, nickel, and zinc. From the other precipitate components of the aluminium group are removed, leaving manganese, cobalt, nickel, and a little zinc (nickel group), and some rare-earth group metals. In the course of analysis of the second precipitate the rare-earth group portion is separated and added to the first precipitate, from which the whole rare-earth group (scandium, thorium, yttrium, lanthanum, cerium, etc.) is extracted before the zirconium group proper is analysed. A variable amount of indium is located in the rare-earth group so that the metal has to be tested for twice.

The method of analysis used here is entirely different. It is supposed that the above precipitates are dissolved in hydrochloric acid and the solutions combined to give a mixture inclusive of all the components of Noyes and Bray's three groups. The mixtures considered here may contain any of *e.g.*, manganese, cobalt, nickel, titanium, zirconium, zinc, indium, scandium, thorium, yttrium, cerium, lanthanum, neodymium, and praseodymium. In portions of them the first five, and sometimes zinc, are tested for directly. Indium and scandium, and zinc in certain circumstances, are detected after they have been freed from interfering elements. In this connection organic solvents as extractants play an important part. As

in earlier papers the experimental conditions described permit the detection of the above metals in accordance with the limits set forth in the summary. Provision is made for the presence of group contaminants, *e.g.*, iron, gallium, and members of the aluminium group. Because of scarcity of material the question of the detection of hafnium, which behaves like zirconium, has not yet been considered, and other rare-earth metals have not been taken into account.

Particulars regarding the isolation of the rare-earth group of metals from one half of the above mixtures, and the subsequent analysis of the group, will, it is hoped, be given later.

Experimental.

Preparation of the Group for Analysis.—Mixtures containing chlorides or nitrates of the various metals and some hydrochloric acid were evaporated just to dryness and taken up in 1 ml. of 6N-hydrochloric acid.

Nickel, Zirconium, and Rare-earth Groups.

(The figures in parentheses are referred to in " Notes on Methods and Tests.")

Solution.—Contains cobalt, manganese, nickel, titanium, zirconium, zinc, indium, scandium, thorium, yttrium, lanthanum, cerium, neodymium, and praseodymium as chlorides in 1 ml. of 6N hydrochloric acid. Test separate portions as follows :

(*a*) Test 1% for Co in a test-tube ($\frac{3}{8}$" × 3"). Make 0·15 ml. of solution, 2N in HCl, add 10—20 mg. of NH_4F and NH_4SCN in large excess. Add 0·2 ml. of *n*-butyl acetate and shake briskly. A blue colour in the ester shows **Co**. Increase the ester to a maximum of 2 ml. when much Co is present. Compare with standards. (1.)

(*b*) Test 1% for Mn in a 5-ml. beaker. Add 0·05 ml. of H_3PO_4 (88%) and expel HCl by evaporating on the hot-plate. Then add 1 ml. of 2N-HNO_3 and 10 mg. of KIO_4, and keep the solution at the boiling point in the covered beaker for at least 15 mins., keeping the volume constant by additions of water. A purple colour shows **Mn**. Centrifuge if necessary and compare with standards. (2.)

(*c*) Test 1% for Ni in a 0·5-ml. centrifuge tube. Add 0·1 ml. of 12% aqueous citric acid and 0·05 ml. of ammonia (*d* 0·88). Heat to 80°, add 0·05 ml. of 5% aqueous dimethylglyoxime (Na salt)—allow more for Co (0·1 ml. per 0·5 mg.)—stir thoroughly, and heat further for 1 min. If a red precipitate due to **Ni** appears, ensure complete precipitation, then centrifuge without cooling, separate the precipitate, dissolve it in 2N-HCl, and reprecipitate as before. Compare with standards. (3.)

(*d*) Test 0·25—1% for Ti on a spotting tile. Add 0·04 ml. of 0·2M-$SnCl_2$ in N-HCl and 0·05 ml. of 1% chromotropic acid in concentrated H_2SO_4. Compare a violet colour, which shows **Ti**, with standards. (4.)

(*e*) Test 5% for Zr in a 1-ml. centrifuge tube. Make 0·25 ml. of solution, 4N in HCl, add 0·05 ml. of perhydrol if Ti is present, heat, and add 0·1 ml. of 4% aqueous *p*-hydroxyphenylarsonic acid. Heat in boiling water for 2 mins. and centrifuge. If a precipitate is present, separate it and add 0·05 ml. of perhydrol and 0·1 ml. of 2N-NaOH. Stir up, centrifuge, separate $Zr(OH)_4$, and dissolve it in 0·1 ml. of 10N-HCl and 0·1 ml. of water. Treat with *p*-hydroxyphenylarsonic acid as before. A white precipitate shows **Zr**. Centrifuge and compare with standards. (5.)

(*f*) Test 10% for Zn. (i) Co absent, Ni < 100 μg. Make 0·25 ml., N in HCl, in a 0·5-ml. centrifuge tube, add 0·01 ml. of 0·01M-$CuSO_4$ and 0·1 ml. of ammonium mercury thiocyanate reagent (30 g. of $HgCl_2$ and 33 g. of NH_4SCN in 100 ml. of water). Stir briskly and centrifuge. A black or violet precipitate shows **Zn** which should be compared with standards. (6.)

(ii) Ni > 100 μg., and/or Co present. Make 0·5 ml., 2N in HCl, in a " Pyrex " test-tube ($\frac{3}{8}$" × 3"), add a large excess of NH_4SCN and 100 mg. of NH_4F, and extract twice with 1 ml. of *n*-butyl acetate. Evaporate the combined extracts, with the aid of an air current, in a " Pyrex " test-tube placed in boiling water. Next cautiously decompose the thiocyanates with concentrated HNO_3, and finally heat in a flame (air current still flowing) until all volatile products are expelled.

If Co is absent, dissolve the residue in 0·25 ml. of N-HNO_3 and test for Zn as in (i). If <500 μg. of Co is present, add 0·2 ml. of water, 0·2 ml. of 2N-NaOH, and a drop of 3% H_2O_2, boil, centrifuge, remove the solution, and add to it 0·04 ml. of concentrated HNO_3. Test for Zn as in (i).

If >500 μg. of Co is present, add to the residue 0·1 ml. of water and just enough 10% aqueous KCN to convert Co into a soluble complex. Add 1 drop of perhydrol and boil for a few mins. to form cobalticyanide. Then add glacial acetic acid in 20% excess by volume, and 0·05 ml. of 10% aqueous potassium cobalticyanide, and heat. If a turbidity appears heat further to coagulate. Separate and wash the precipitate, which may be zinc cobalticyanide, without stirring it up, in 2N-acetic acid. To confirm Zn add to the precipitate 0·05 ml. of 4N-H_2SO_4, heat until fumes of H_2SO_4 appear and the precipitate is dissolved, and proceed with the removal of Co and the final test for Zn as above. (7.)

(*g*) Test 10% for In and Sc in a test-tube ($\frac{3}{8}$" × 3"). Add 0·05 ml. of 10N-HCl, 0·05 ml. of water, and 0·3 ml. of 10% aqueous cupferron. Extract thrice with 1 ml. of chloroform. To the residual aqueous layer add a large excess of NH_4SCN and extract twice with 1 ml. of *n*-butyl acetate. Wash the combined extracts with 0·05 ml. of 2N-HCl, saturated with NH_4SCN. Expel the ester, destroy thiocyanates, and remove volatile products as described under (*f*, ii). Dissolve the residue in 0·15 ml. of water, make approximately neutral, and add sufficient 10% aqueous KCN to convert Co and Zn into soluble complexes. Add a drop of perhydrol, boil, add a few drops of 2N-NaOH, and reboil for a short time. If a precipitate [$In(OH)_3$ and $Sc(OH)_3$] appears, separate it, wash it with hot water, and dissolve it in 0·5 ml. of 2N-acetic acid. (8.)

(i) Test for In. Into the hot solution pass H_2S for 10 mins. A yellow precipitate shows **In**. Centrifuge and determine it. If desired, confirm a small precipitate, after washing it, with alizarin. (9.)

(ii) Test for Sc in the centrifugate from In_2S_3. H_2S must be absent for test (β).

(α) To 0·25 ml. of 2N-acetic acid add 0·01 ml. of 1% aqueous alizarin-S and 0·05 ml. of the test

solution, and set aside for 5 mins. If no pink colour is observed add more test solution gradually up to a maximum of 0·25 ml., and more reagent if necessary. If a pink colour due to **Sc** appears readily, add additional reagent gradually. Should the colour become too deep a red, repeat the experiment with less of the test solution. Compare with standards. Allow 20 mins. for full colour development. (10.)

(*β*) To 0·25 ml. of 2N-acetic acid add 0·01 ml. of morin (0·02% in acetone) with which **Sc** shows a green fluorescence in ultra-violet light. Gradually add the test solution, up to a maximum of 0·25 ml. if necessary, until a match is obtained with a standard containing between 1 and 50 μg. of Sc. (11.)

(*h*) Reserve 50% for the isolation of the rare-earth group.

Notes on Methods and Tests.—The experimental technique has been described in earlier papers of the series.

Note 1. The amount of ammonium thiocyanate was such that some remained undissolved throughout the extraction process. The ammonium fluoride masked titanium (0·5 mg.) and group contaminants, *e.g.*, iron, vanadium, and uranium. 0·5 μG. of cobalt was detectable in 0·2 ml. of ester. The extraction of cobalt was highly efficient, and 2 ml. of ester were used merely when the colour was otherwise too dark for matching purposes. The detection of 1 μg. of cobalt was not affected by the presence of at least 1 mg. of any of its associates, or of any member of the aluminium group (Al, Be, Cr^{VI}, W^{VI}, U^{VI}, V^{V}), or of iron or gallium. Cobalt was not retained by the precipitated fluorides of the rare-earth metals.

Note 2. The limit of identification of manganese was 0·5 μg., and 50 μg. was the maximum desirable for the comparison of colours. The solution could be further diluted with water. 2 μG. of manganese were found in association with 1 mg. of any of the elements mentioned in Note 1, except chromium (VI), of which only 100 μg. were permissible without the preparation of a blank experiment. Phosphate precipitates deposited by titanium, zirconium, and cerium, especially the last, tended to retain a little manganese.

Note 3. Ammonium citrate held all the metals in solution. 0·5 μG. of nickel was detectable. Excess of dimethylglyoxime commonly separated out from cold solutions without seriously affecting estimations. Nickel was detectable in association with at least a 1000-fold excess of the metals cited in Note 1, including cobalt, if sufficient reagent was present. Iron and cobalt together may form a brown precipitate with dimethylglyoxime. 25 μG. of iron, which is much more than one would expect to have here, did not upset the detection of 1 μg. of nickel in the presence of 1 mg. of cobalt, if prolonged boiling was avoided. Reprecipitation of the nickel complex corrected for a marked diminution in the bulk of the precipitate, caused by other metals and especially cobalt.

Note 4. The final concentration of 50% sulphuric acid was chosen because, at lower concentrations, the sensitivity of the test was reduced, and, at much higher concentrations, the chromotropic acid itself gave too pronounced a colour, probably because of impurity. Stannous chloride prevented or reduced the interference of iron, vanadium, tungsten, and uranium. 0·5 μG. was just detectable, and 25 μg. were set as a maximum for determinations and for the amount of reagent recommended. Colours did not deteriorate within two hours. 2 μG. of titanium were detectable in the presence of at least a 1000-fold excess of any component of the group, or of aluminium, beryllium, gallium, or zinc; and 5 μg., with a 100-fold excess of chromium, iron, uranium, or vanadium, or a 10-fold excess of tungsten.

Note 5. This test was used for the detection of zirconium in the tantalum group. Precipitation was best effected in a solution 2—5N in hydrochloric acid, and 1 μg. of zirconium was just detectable. The maximum amount of titanium under consideration was held adequately in solution by perhydrol, provided that heating was not prolonged. The titanium complex, if inadvertently deposited, was readily soluble in a drop of hydrochloric acid and a drop of perhydrol, whereas even a small precipitate of the zirconium complex remained undissolved. Other metals in the solution might reduce the bulk of the complex. The reprecipitation process prevented under-estimation, and at the same time eliminated any titanium that might have been carried down. 5—10 μG. of zirconium were found in association with 100 times the amount of titanium. 2 μG. were detectable in the presence of at least a 1000-fold excess of any other group component, and also of iron, gallium, aluminium, beryllium, chromium, uranium, or vanadium.

Note 6. Zinc was detected in the aluminium group by this method. Nitric acid solutions are said to give superior results, but tests made in hydrochloric acid solution were very satisfactory also, 2 μg. of zinc being found. 10 μG. of zinc were detectable in association with at least a 100-fold excess of scandium, and a 500-fold excess of manganese, indium, zirconium, gallium, iron (more reagent needed), or rare-earth group metals. Only a 100-fold excess of titanium, which hindered the deposition, was permissible. Nickel greatly hindered the precipitation and a 5-fold excess only could be tolerated. Cobalt reacted with ammonium mercury thiocyanate and, in the presence of copper sulphate, violet and black precipitates like those for zinc might be obtained. Consequently cobalt had to be completely removed before zinc was tested for.

Note 7. The extraction of cobalt and zinc from thiocyanate–fluoride solutions by means of *n*-butyl acetate was essentially complete, and practically nothing except a little indium accompanied them, even when the maximum amounts of other metals were present. After the destruction of thiocyanates, and when cobalt was absent, the direct test for zinc was applicable. Experiments made with 25 μg. of zinc in association with varying amounts of cobalt showed that the separation of 0·5 mg. of the latter by means of sodium hydroxide involved the loss of 40% of the zinc. When, therefore, more than 0·5 mg. of cobalt was present it was converted into cobalticyanide, and zinc precipitated as zinc cobalticyanide. As a precipitate might be produced by traces of other metals, it was essential to dissolve it, separate cobalt, and test for zinc as above. In mixtures containing in addition to 25 μg. of zinc, 5 mg. of cobalt, nickel, manganese, or rare-earth group metals, or 1 mg. of each of titanium, zirconium, indium, and scandium, the amounts of zinc retrieved were 12, 10, 10, 20, and 25 μg., respectively. The low results were attributed to difficulty in recovering all the zinc cobalticyanide, which was very finely divided and separated extremely slowly.

Note 8. For indium and scandium no direct tests applicable in the presence or any or all of the group components were found. The tests for scandium required the absence of a great many elements, and that for indium, a considerable number. The series of simple operations prescribed separated indium and scandium, with comparatively little loss, from all the other members of the group and likely contaminants. For instance, cupferron and chloroform eliminated titanium, zirconium, iron, gallium, vanadium, and some rare-earth metals (Lundell and Hoffman, "Outlines of Methods of Chemical Analysis," 1938, 118). The butyl acetate extract contained indium, scandium, zinc, and cobalt, and contaminants, *e.g.*, aluminium, beryllium, uranium, and tungsten. By means of potassium cyanide and sodium hydroxide all of these except indium and scandium, which were precipitated as hydroxides, were taken into solution.

Note 9. The above separation of indium and scandium was so satisfactory that the precipitation of indium sulphide sufficed for the detection of the element, 5 μg. being readily found. For a doubtful test [precipitate too pale (ZnS), or discoloured (CoS)] confirmation by means of alizarin (Wenger, *Helv. Chim. Acta*, 1945, **28**, 539) is recommended. The hydrochloric acid solution of the precipitate is spotted on drop-reaction paper which has been impregnated with alizarin (0·2% in alcohol), and the spot developed over concentrated ammonia. The paper is then momentarily dipped in 10% aqueous potassium cyanide and finally soaked in saturated aqueous boric acid. Indium leaves a violet-pink spot. The cyanide destroys colours initially produced by zinc and cobalt.

Note 10. The test with alizarin-S (Beck, *Mikrochim. Acta*, 1937, **2**, 9) must be made in a weakly acid solution. The colour develops slowly and its depth varies with the acid concentration. In 2N-acetic acid interference from rare-earth metals is prevented, and that from other metals minimised. Indium did not itself react but, in the presence of scandium, it intensified the colour. The limit of identification of scandium was 2 μg., and amounts in excess of 25 μg. gave too deep colours for determination. 25 μG. of scandium required fully 0·1 ml. of the reagent. An excess is undesirable because of its own colour.

Note 11. This test was described by Beck (*loc. cit.*). Under the prescribed conditions 1 μg. of scandium was detectable. For determinations the upper limit was 50 μg. Many other elements fluoresced, *e.g.*, thorium, zirconium, yttrium, indium, gallium, aluminium, beryllium, and zinc. A few quenched the fluorescence of scandium. The method of isolating scandium was, however, so satisfactory that the brightest fluorescence noted in mixtures containing 5 mg. of other elements, and no scandium, corresponded to <2 μg. of scandium.

Analysis of Mixtures.—Eight mixtures were analysed in order to test the validity of the scheme. All contained, in addition to the normal group components, 0·5 mg. of each of iron, gallium, aluminium, and vanadium as contaminants. No. 5 contained 40 mg. of rare-earth group metals (Th, Y, Ce, La, and Pr); No. 7, 8 mg. of thorium and 1 mg. of lanthanum; and No. 8, 1 mg. of yttrium. The results shown in the table are the estimated weights in mg. of the metals found. Where these differed from the weights taken, the latter are shown in parentheses.

	Co.	Ni.	Mn.	Zn.	Ti.	Zr.	In.	Sc.
1	33 (44)	0·2 (0·25)	0	0·1 (0·25)	0·2 (0·25)	0·7 (1)	0	0·1 (0·25)
2	0·25	0·25 (0·5)	34 (28)	1 (2)	0·4 (0·5)	3 (4)	0·4 (0·5)	0·5
3	5 (6)	14 (12)	6 (7)	0	2·5 (4)	8 (9)	7 (6)	3 (4)
4	0·5	0	0·4 (0·5)	0	0	0·5	0·5 (1)	5 (7)
5	1·75 (1)	1·5 (2)	3	0·15 (0·25)	6	0	0·3 (0·5)	0·15 (0·25)
6	0	1·75 (1)	0	0	1	0	7 (10)	0·5 (1)
7	43 (32)	0	0·25	0·5 (1)	0	0	0	0
8	0	27 (36)	0·7 (1)	1 (0·5)	1 (0·5)	0·2 (0·25)	0·2 (0·25)	0

The results were considered satisfactory, and all the tests, except that for zinc in the presence of much cobalt, were expeditiously carried out. It would be a great advantage if one had a sensitive test applicable to the detection of zinc in these circumstances.

I am indebted to the Trustees of the Moray Fund for a Grant which has been used for the purchase of highly purified chemicals.

THE UNIVERSITY, EDINBURGH, 9. [*Received, December 16th*, 1946.]

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250. *Magnetic Studies on Polymerisation. Part I. Magnetic Optical Rotatory Powers and Diamagnetic Susceptibilities of Certain Polymethyl Methacrylates.*

By (MISS) M. E. BEDWELL.

The magneto-optic rotatory powers and diamagnetic susceptibilities of methyl methacrylate and the polymethyl methacrylates have been measured. The results may be employed to calculate the average molecular weights of the polymers, fair agreement being obtained with values determined by a viscosity method (Schulz and Blaschke).

THE magnetic susceptibility method which Farquharson (*Trans. Faraday Soc.*, 1936, **32**, 219) employed to investigate the degree of polymerisation of 2:3-dimethylbutadiene and other substances, is used in the present investigation on the polymethyl methacrylates. In addition,

another method of molecular weight determination is proposed, which is based in the magneto-optical rotatory powers of the polymers concerned.

Melville and others (General Discussion, *Trans. Faraday Soc.*, 1944, **40**, 217—273) have surveyed the end-group, osmotic, and viscosity methods for the determination of the molecular weight of higher polymers; of these, Schulz and Dinglinger (*J. pr. Chem.*, 1940, **157**, 15), Schulz and Blaschke (*Z. physikal. Chem.*, 1942, *B*, **51**, 75), Baxendale, Bywater, and Evans (*J. Polymer Sci.*, 1946, **1**, 237), and Walling and Briggs (*J. Amer. Chem. Soc.*, 1946, **68**, 1141) have shown that the viscosity method can be usefully employed to find the molecular weights of the polymethyl methacrylates, using modifications of the Staudinger equation; the present results are compared with those obtained by Schulz and Blaschke in their detailed study of the benzoyl peroxide-catalysed polymerisation of methyl methacrylate.

Magnetic Optical Rotatory Powers.—Perkin (*J.*, 1884, **45**, 421 *et seq.*) deduced from measurements on many homologous series of organic compounds that the molecular magnetic rotation M of a substance could be expressed by

$$M = S + n\Delta \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where Δ is the increase in rotation between successive members of an homologous series (the "CH_2 increment") which Perkin found experimentally to have a mean value of 1·023; n is the number of carbon atoms in the molecule; S is the "series constant" which Perkin obtained by subtracting the value of $n\Delta$ from the total observed rotation, the resulting figure being approximately constant for an homologous series of compounds and different for different series.

It was proposed to make use of this relationship in the estimation of molecular weights of higher polymers.

It follows from the above equation that a monomer is related to its polymer thus:

$$M_p = n_a M_m + (n_a - 1)S_1 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

where M_p, M_m are the molecular magnetic rotations of polymer and monomer respectively, n_a is the average number of units in the molecule of polymer, and S_1 is the "series constant", which is in this case Perkin's constitutive correction for the formation of a new bond.

By definition,

$$M_p = \theta_p w_p/w; \quad M_m = \theta_m w_m/w$$
$$\theta_p = \alpha_p d/\alpha d_p; \quad \theta_m = \alpha_m d/\alpha d_m$$

where α_p, α_m, α are the observed rotations of polymer, monomer, and water respectively under the same conditions; θ_p, θ_m are the specific rotations of polymer and monomer, respectively; w_p, w_m, w are the molecular weights of polymer, monomer, and water, and d_p, d_m, d are the corresponding densities measured at the same temperature.

But $w_p = n_a \times w_m$, therefore

$$\theta_p n_a w_m/w = n_a \theta_m w_m/w + (n_a - 1)S_1 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

Hence n_a may be calculated from the experimental results.

Diamagnetic Susceptibilities.—Farquharson's expression for the mass susceptibility of a polymer is

$$\chi_s = [n_a \chi_B + (n_a - 1)\lambda]/n_a w_m \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

where w_m is the molecular weight of the monomer, χ_s is the mass susceptibility of the polymer, χ_B is the molecular susceptibility of the monomer, n_a is the degree of polymerisation, and λ is Pascal's constitutive correction constant for the bond ruptured. This equation is used for the calculation of n_a.

Average Molecular Weights.—The following table has been drawn up from measurements of magneto-optic rotatory powers and diamagnetic susceptibility which are listed later (Tables I and II); t is the polymerisation time; n_a is the average number of units in the molecule of polymer, and w_p the corresponding average molecular weight, calculated from equations (3) and (4).

	Magneto-optic rotation.			Diamagnetic susceptibility.		
t (mins.).	n_a.	$n_a\theta_p$.	w_p.	n_a.	$n_a\chi_s$.	w_p.
0	1	1·093	100	1	0·5370	100
15	2	2·088	190	1—2	0·7521	130
30	2—3	2·535	240	2—3	1·248	220
45	4	4·279	410	3—4	2·192	380
60	5	5·556	550	5	2·904	500
75	14	13·77	1390	14	8·809	1380
180	68	66·80	6750	61 *	36·06	6110
				61 *	36·06	6110

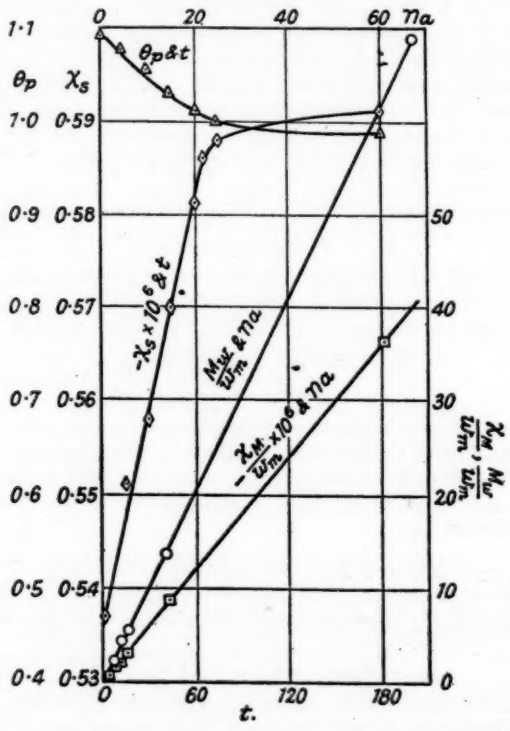
* Measurements on powder and solution, respectively.

A value of − 1·112 was used for S_1 in equation (3), by analogy with ethyl crotonate, for which Perkin found an increase of rotation of 1·112 compared with ethyl butyrate; λ was assumed to be + 5·5, which is Pascal's constitutive correction for the double bond.

The decrease in magneto-optic rotation and the increase in magnetic susceptibility which are found experimentally during polymerisation (Tables I and II) would be expected from the sign of the constants S_1 and λ above.

It will be seen that the figures for n_a and w_p obtained by the two methods agree very closely.

Extrapolation of the data of Schulz and Blaske to 80° and the benzoyl peroxide concentration used in the present investigation gives an upper limit of 5000—6000 for the molecular weight from viscosity measurements. Walling and Briggs quote higher figures in their determinations on benzoyl peroxide-free quinol-stabilised methyl methacrylate, and by analogy, an upper limit of 7000—8000 for the molecular weight may be estimated. The present figures (6750, 6110) are of the same order as the above, but from the calculation employed, it is obvious that decreasing accuracy is possible with polymers of molecular weights of the order 10^5 or higher.



Walling and Briggs found that, at 131°, concentrations of quinol of less than 1% had little effect on the molecular weight of the polymer, and it is doubtful whether the present concentration (0·03%) would cause alteration of the molecular weight to any appreciable extent at 80°.

Complete agreement is not to be expected, since both the present methods give the number-average molecular weight w_n, whereas the viscosity method gives the weight-average molecular weight w_w:

$$w_n = \Sigma w_i N_i / \Sigma N_i \text{ and } w_w = \Sigma w_i N_i / \Sigma w_i N_i$$

w_i is the molecular weight averaged over the number of particles, and N_i is the number of particles of chain length i (Mark and Raff, " Higher Polymeric Reactions," New York, 1941).

Course of Polymerisation.—The polymerisation of methyl methacrylate may be explained by a chain mechanism (Mark, " Physical Chemistry of Higher Polymeric Systems ", New York, 1940, 309). The methyl methacrylate molecule is thought to become activated, by heat, light, or catalyst, and in this condition it accumulates other methyl methacrylate molecules to form a long chain. Eventually the macro-molecule becomes deactivated by the saturation of the free valencies at the growing ends.

Alyea, Gartland, and Graham (*Ind. Eng. Chem.*, 1942, **34**, 458) have shown that benzoyl peroxide initiates these reaction chains, whereas quinol breaks the chains, and in doing so becomes oxidised to benzoquinone. Strain (*Ind. Eng. Chem.*, 1938, **30**, 345) has examined the polymerisation of methyl methacrylate in various organic solvents, using varying quantities of benzoyl peroxide as catalyst.

If the polymerisation is straightforward, χ_s and t will show a hyperbolic relationship (as Farquharson found to be the case with 2 : 3-dimethylbutadiene) and the curve for θ_p and t should also be a hyperbola. This was found to hold true in the present case (see Fig.). These results are consistent with Strain's hyperbolic percentage polymer yield–rate curves for 20% solutions of methyl methacrylate in benzene, acetone, and other solvents.

The figure also shows the linear relationships between $M_w/w_m(= n_a\theta_p)$ and n_a, and between $\chi_m/w_m(= n_a\chi_s)$ and n, in accordance with equations (3) and (4).

Experimental.

Measurement of Magneto-optic Rotations.—The apparatus used in these measurements has been described by Anderson, Bedwell, and Le Fèvre (this vol., p. 457). Methyl methacrylate was polymerised at 80° in the presence of a catalyst (1 mole of benzoyl peroxide to 500 moles of monomer). Samples were withdrawn at intervals, and the magneto-optic rotation measured at 20°. For the final determination, a 20% solution in methylene chloride was used. The results are shown in the figure and in Table I; t is the polymerisation time; w_1 is the weight fraction of the solute in the solution; d_{12} and α_{12} are the respective relative density and observed rotation of pure solute or solution.

By the additivity rule, $\theta_1 = (\theta_{12} - \theta_2)/w_1 + \theta_2$, where θ_1, θ_2, θ_{12} are the specific rotations of solute, solvent, and solution, respectively.

Table I.

t (mins.).	$100w_1$.	$(d_{12})^{20°}_{20°}$.	α_{12}.	α_{12}/α.	α_1/α.	θ_1.	
Water.							
0	0	0·99820	8·80	—	—	—	
Methylene chloride.							
0	0	1·33898	10·80	1·228	1·228	0·919	
Methyl methacrylate.							
0	100	0·96698	9·32	1·057	1·057	1·093	
15	100	0·97641	9·24	1·050	1·050	1·076	
30	100	0·98502	9·16	1·042	1·042	1·056	
45	100	0·99773	9·04	1·030	1·030	1·032	
60	100	1·00788	8·96	1·018	1·018	1·012	θ_p
75	100	1·01619	8·88	1·008	1·008	0·992	
180	20·04	1·31487 *	10·72	1·227	1·173	0·989	

* $(d_1)^{20°}_{20°} = 1·18630$.

Measurement of Magnetic Susceptibility.—Measurements were made at 20°, using the Gouy apparatus described by Anderson, Bedwell, and Le Fèvre (*loc. cit.*). The process of polymerisation was catalysed by benzoyl peroxide at 80°, as described in the previous section. Samples were withdrawn at intervals for measurement. The final polymer was measured both in 18% solution and in the finely powdered state. The results are shown in the figure and in Table II; t is the polymerisation time, and χ_s is the specific susceptibility of the polymerising substance.

Table II.

t (mins.)	0	15	30	45	60	66	75	180
χ_s	0·5370	0·5511	0·5670	0·5776	0·5809	0·5860	0·5881	0·5909 *
								0·5909 *

* Measurements on powder and solution respectively.

Purification of Methyl Methacrylate.—The methyl methacrylate was as supplied by I.C.I. Ltd. stabilised with quinol (0·5%). It was fractionally distilled under reduced pressure and the fraction retained ($n_D^{20°}$ 1·4143) was frozen at −70°, redistilled under high vacuum (after Walling and Briggs), and stored at −70° in the dark, with the addition of quinol as stabiliser, in the proportion of 1 mole of quinol to 4000 moles of methyl methacrylate.

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Royal Aircraft Establishment,
Farnborough, Hants.

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251. *Synthetic Antimalarials. Part XXI. 4-Arylamino-6-aminoalkylaminopyrimidines. Further Variations.*

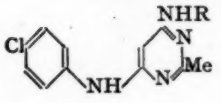
By F. R. Basford, F. H. S. Curd, E. Hoggarth, and F. L. Rose.

An alternative method of synthesis has been devised for the inactive 4-arylamino-6-aminoalkylamino-2-methylpyrimidines (type I) described in Part VIII (*J.*, 1946, 713), and, employing both this and the original route, substituents such as methyl, ethyl, and phenyl have been introduced into position 5 of the pyrimidine nucleus. These new derivatives were inactive, as were also related compounds in which the 2-methyl group was replaced by amino-.

The importance of the aminoalkylamino-side chain in the active 2-arylamino-4-aminoalkylamino- and 4-arylamino-2-aminoalkylamino-6-methylpyrimidines described earlier in this series (*J.*, 1946, 343, 351, 366, 370, 378) has been shown by the lack of activity in compounds, now synthesised, in which that grouping is replaced by primary amino-.

Differences in chemical reactivity of several related chloropyrimidine derivatives are discussed.

Chronologically the work described in this paper follows that reported in Part VIII (*J.*, 1946, 713) which concerned the synthesis of a variety of 4-arylamino-6-aminoalkylamino-2-methylpyrimidines including compounds of type (I; R = dialkylaminoalkyl). All these compounds were found to be without activity against *P. gallinaceum* in chicks. In the same paper we drew attention to the fact that in compounds of type (I) there do not exist two amidine units capable of independent tautomerism as are found in the two isomeric types (II) and (III).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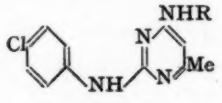
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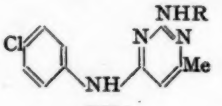
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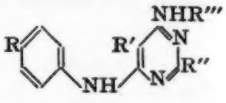
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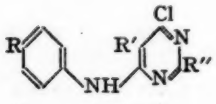
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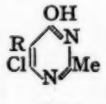
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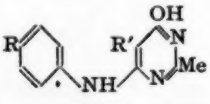
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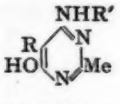
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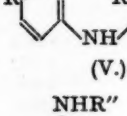
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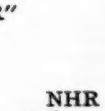
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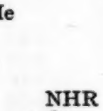
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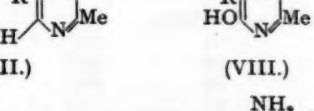
(XII.)

Since one important development of our work (see Part X, *J.*, 1946, 729) was in part based on the recognition of the possible significance of this difference, it seemed desirable to demonstrate with as much certainty as possible that antimalarial activity could not be developed in compounds of type (I). Thus, for example, in a series of simple 2-amino-4-aminoalkylaminopyrimidines, Hull, Lovell, Openshaw, Payman, and Todd (*J.*, 1946, 357) have shown that the introduction of a substituent into position 5 of the pyrimidine nucleus induced antimalarial activity. Clearly, this was a device that needed to be tried in the present instance, although it was appreciated that the two cases might not be comparable since it had been suggested (*idem, ibid.*) that the activity of the simple pyrimidines might be associated with an interference with nucleoside synthesis and the 5-substituent gave a closer structural resemblance to the purines, whereas we in the past have stressed the relationship of the anilinopyrimidines to riboflavin. The new preparations were of type (IV; R′ = Me, Et, or Ph; R″ = Me). Not all of these were made by the general method described in the earlier paper, namely through the reaction of an aminoalkylamine with the appropriately substituted 4-chloro-6-arylamino-2-methylpyrimidine (V; R″ = Me), itself obtained either directly by condensing a 4 : 6-dichloro-2-methylpyrimidine with an arylamine, or indirectly from a 4-chloro-6-hydroxy-2-methylpyrimidine (VI) by interaction with an arylamine followed by treatment of the resulting 4-arylamino-6-hydroxy-2-methylpyrimidine (VII) with phosphoryl chloride. A useful alternative method of synthesis has now been developed in which the arylamino- and aminoalkylamino-groups are introduced in the reverse order. The method is best illustrated by its application to the original type (I). β-Diethylaminoethylamine and γ-diethylaminopropylamine when heated with 4-chloro-6-hydroxy-2-methylpyrimidine (VI; R = H) gave respectively

4-β-diethylaminoethylamino- (VIII; R = H, R′ = $[CH_2]_2$·NEt_2) and 4-γ-diethylaminopropylamino-6-hydroxy-2-methylpyrimidine (VIII; R = H, R′ = $[CH_2]_3$·NEt_2) as their *hydrochlorides*. Treatment of these hydrochlorides with boiling phosphoryl chloride converted them into *4-chloro-6-β-diethylaminoethylamino-* (IX; R = H, R′ = Me, R″ = $[CH_2]_2$·NEt_2) and *4-chloro-6-γ-diethylaminopropylamino-2-methylpyrimidine* (IX; R = H, R′ = Me, R″ = $[CH_2]_3$·NEt_2) respectively. When a similar series of reactions was tried starting with δ-diethylamino-α-methylbutylamine it was found impossible to crystallise the intermediate 4-δ-diethylamino-α-methylbutylamino-6-hydroxy-2-methylpyrimidine hydrochloride, but treatment of the crude product with phosphoryl chloride gave 4-chloro-6-δ-diethylamino-α-methylbutylamino-2-methylpyrimidine (IX; R = H, R′ = Me, R″ = CHMe·$[CH_2]_3$·NEt_2) in good yield. The above compounds of type (IX) underwent smooth reaction with *p*-chloroaniline in boiling aqueous solution as their monohydrochlorides in presence of a little extra hydrochloric acid, to give the corresponding 4-*p*-chloroanilino-6-dialkylaminoalkylamino-2-methylpyrimidines (I; R = $[CH_2]_2$·NEt_2, $[CH_2]_3$·NEt_2, or CHMe·$[CH_2]_3$·NEt_2) described in Part VIII (*loc. cit.*). In these reactions with *p*-chloroaniline no obvious differences could be detected between the reactivity of the 4-chloro-6-dialkylaminoalkylamino-2-methylpyrimidines and the isomeric 2-chloro-4-dialkylaminoalkylamino-6-methylpyrimidines (X) (see Part XV, this vol., p. 783) and 4-chloro-2-dialkylaminoalkylamino-6-methylpyrimidines (XI) (Part VI, *J.*, 1946, 370). No appreciable condensation occurred, even in the last two instances, when the chloropyrimidines were employed as free bases with addition of a trace of hydrochloric acid. The need for slightly more than one equivalent of acid to facilitate the reaction suggested that the chlorine atom was only labile after salt formation had occurred on the dialkylamino-group of the side chain.

A comparison with the three isomeric types of chlorodialkylaminoalkylaminomethylpyrimidines was provided by the corresponding unsubstituted amino-compounds. Like 2-chloro-4-amino- (X; R = H) and 4-chloro-2-amino-6-methylpyrimidine (XI; R = H), 4-chloro-6-amino-2-methylpyrimidine (IX; R = R″ = H, R′ = Me) reacted readily with *p*-chloroaniline in boiling aqueous solution in presence of only a little hydrochloric acid. The apparent normal reactivity of the 4-chloro-6-amino- and 4-chloro-6-dialkylaminoalkylamino-2-methylpyrimidines in comparison with their respective isomers was in direct contrast to that of the 4-chloro-6-arylamino-2-methylpyrimidines (IX; R = H, R′ = Me, R″ = aryl) which were found to be less reactive than the corresponding 2-chloro-4-arylamino- (X; R = aryl) and 4-chloro-2-arylamino-6-methylpyrimidines (XI; R = aryl) (see Part VIII, *loc. cit.*). This conforms with the suggestion there advanced that in arylaminopyrimidines there is a strong tendency for the linking nitrogen atom to conjugate with the benzene ring.

Several points may be noted in connection with the synthesis of compounds of type (IV; R″ = Me) described in detail in the experimental section. In the preparation of *4-chloro-6-p-anisidino-2 : 5-dimethylpyrimidine* (V; R = OMe, R′ = R″ = Me), required for the synthesis of (IV; R = OMe, R′ = R″ = Me, R‴ = $[CH_2]_2$·NEt_2), by condensation of 4 : 6-dichloro-2 : 5-dimethylpyrimidine with *p*-anisidine in aqueous acetone catalysed by hydrochloric acid, no formation of di-condensation product was observed. Even the use of two molecular proportions of *p*-anisidine gave exclusively 4-chloro-6-*p*-anisidino-2 : 5-dimethylpyrimidine in contrast to the formation mainly of 4 : 6-di-*p*-anisidino-2-methylpyrimidine from 4 : 6-dichloro-2-methylpyrimidine and two equivalents of *p*-anisidine under identical conditions (see Part VIII). This steric effect of a 5-substituent was also noticed during the synthesis of *4-p-chloroanilino-6-γ-diethylaminopropylamino-2-methyl-5-ethylpyrimidine* (IV; R = Cl, R′ = Et, R″ = Me, R‴ = $[CH_2]_3$·NEt_2). Whereas, as noted above, compounds of type (IX; R′ = Me, R″ = dialkylaminoalkyl) containing no substituent in the 5-position (R = H) condensed readily on boiling with *p*-chloroaniline in aqueous solution containing a little more than one equivalent of hydrochloric acid, no corresponding condensation occurred between *4-chloro-6-γ-diethylaminopropylamino-2-methyl-5-ethylpyrimidine* (IX; R = Et, R′ = Me, R″ = $[CH_2]_3$·NEt_2) and *p*-chloroaniline under similar conditions. Higher temperatures were found to be necessary to effect condensation. The steric effect of a 5-phenyl group was even more marked than that of methyl or ethyl. Thus the reaction of *p*-chloroaniline with *4 : 6-dichloro-5-phenyl-2-methylpyrimidine* to give *4-chloro-6-p-chloroanilino-5-phenyl-2-methylpyrimidine* (V; R = Cl, R′ = Ph, R″ = Me) failed completely in boiling aqueous acetone with added hydrochloric acid, gave small yields in boiling alcohol, but succeeded at 115—120° in an equivalent of acetic acid. Tests using *P. gallinaceum* in chicks, carried out by our colleague, Dr. D. G. Davey, with the compounds of type (IV; R″ = Me), showed that the introduction of a substituent into the 5-position of type (I) failed to confer antimalarial activity.

The necessity for the aminoalkyl group (R) in types (II) and (III) to promote antimalarial

activity was shown by the inactivity in the same test of 4-*amino*-2-p-*chloroanilino*- (II; R = H) and 2-*amino*-4-p-*chloroanilino*-6-*methylpyrimidine* (III; R = H). The former was made by condensing (X; R = H) with *p*-chloroaniline, as mentioned above, and also by the action of ammonia on 4-chloro-2-*p*-chloroanilino-6-methylpyrimidine at 140—150°. When, however, the action of ammonia on 4-chloro-2-*p*-chlorophenylguanidino-6-methylpyrimidine was tried with a view to the preparation of (XII), in order to assess the need for the aminoalkyl group in the active 2-*p*-chlorophenylguanidino-4-aminoalkylamino-6-methylpyrimidines described in Part IV (*J.*, 1946, 362), it was found that 2-amino-4-*p*-chloroanilino-6-methylpyrimidine was the main product. Hydrolysis of 2-*p*-chlorophenylguanidino-4-β-diethylaminoethylamino-6-methylpyrimidine with N-hydrochloric acid has been shown by Spinks and Tottey (*Ann. Trop. Med. Parasit.*, 1945, **39**, 190) to give *p*-chloroaniline, 2-amino-4-β-diethylaminoethylamino-6-methylpyrimidine, ammonia, and carbon dioxide. Analogously, it is suggested that 4-chloro-2-*p*-chlorophenylguanidino-6-methylpyrimidine by ammonolysis gave *p*-chloroaniline and 4-chloro-2-amino-6-methylpyrimidine which then interacted to yield (III; R = H).

As a further extension of the investigation of compounds of type (IV) it seemed desirable to study compounds containing an amino-group in the 2-position (R″ = NH_2). The presence of such a group, in association with the anilino-residue, would provide the two linked independent amidine units which are a feature of types (II) and (III) without reference to the aminoalkylamino-group, and the only function required of the latter would be that of conditioning the pharmacology of the drug molecule.

Like 4 : 6-dichloro-2-methylpyrimidine, 4 : 6-dichloro-2-aminopyrimidine reacted with *p*-chloroaniline in boiling aqueous acetone in presence of a little hydrochloric acid as catalyst to give 4-*chloro*-2-*amino*-6-p-*chloroanilinopyrimidine* (V; R = Cl, R′ = H, R″ = NH_2). This condensed smoothly with dialkylaminoalkylamines at 150—160°. In this way the following were prepared: 2-*amino*-4-p-*chloroanilino*-6-β-*diethylaminoethylamino*- (IV; R = Cl, R′ = H, R″ = NH_2, R‴ = $[CH_2]_2{\cdot}NEt_2$) and 2-*amino*-4-p-*chloroanilino*-6-γ-*diethylaminopropylamino-pyrimidine* (IV; R = Cl, R′ = H, R″ = NH_2, R‴ = $[CH_2]_3{\cdot}NEt_2$) and the corresponding compounds containing the β-dimethylaminoethylamino-, γ-dimethylaminopropylamino-, and δ-diethylamino-α-methylbutylamino- side chains. 2-Amino-4-*p*-chloroanilino-6-β-diethylaminoethylaminopyrimidine was also obtained by reaction of *p*-chloroaniline hydrochloride with 4-*chloro*-2-*amino*-6-β-*diethylaminoethylaminopyrimidine* (IX; R = H, R′ = NH_2, R″ = $[CH_2]_2{\cdot}NEt_2$) which resulted from condensation of β-diethylaminoethylamine with 4 : 6-dichloro-2-aminopyrimidine. The former method of synthesis was also employed for the preparation of 2-*amino*-4-p-*anisidino*- (IV; R = OMe, R′ = H, R″ = NH_2, R‴ = $[CH_2]_2{\cdot}NEt_2$) and 2-*amino*-4-p-*toluidino*-6-β-*diethylaminoethylaminopyrimidine* (IV; R = Me, R′ = H, R″ = NH_2, R‴ = $[CH_2]_2{\cdot}NEt_2$).

None of these compounds containing an amino-group in the 2-position of the pyrimidine nucleus exhibited any antimalarial activity, nor did any of the several 5-ethyl or 5-phenyl derivatives which were prepared (*vide infra*). Similar lack of activity characterised a series of 4-chloro-2-amino-6-aminolkylamino-5-ethyl- and -phenyl-pyrimidines which thus resemble the related 4-chloro-2-amino-6-dialkylaminoalkylamino-5-methylpyrimidines investigated by Hull, Lovell, Openshaw, and Todd (Part XI, this vol., p. 41).

Experimental.

4-β-Diethylaminoethylamino-6-hydroxy-2-methylpyrimidine (VIII; R = H, R′ = $[CH_2]_2{\cdot}NEt_2$).—4-Chloro-6-hydroxy-2-methylpyrimidine (14·4 g.) (Part VIII, *loc. cit.*) and β-diethylaminoethylamine (11·6 g.) were heated at 150—160° for 8 hours to give *4-β-diethylaminoethylamino-6-hydroxy-2-methylpyrimidine hydrochloride* which separated from moist alcohol–ethyl acetate as a hydrate which did not lose water on drying at 100°; colourless laminæ, m. p. 193—195° (Found: C, 47·9; H, 7·9; N, 20·7; Cl′, 13·0. $C_{11}H_{20}ON_4,HCl,H_2O$ requires C, 47·4; H, 7·5; N, 20·1; Cl′, 12·8%).

4-γ-Diethylaminopropylamino-6-hydroxy-2-methylpyrimidine (VIII; R = H, R′ = $[CH_2]_3{\cdot}NEt_2$).—By substituting γ-diethylaminopropylamine for the β-diethylaminoethylamine in the above preparation this was obtained as its *monohydrochloride* which crystallised from alcohol–ethyl acetate as colourless needles, m. p. 87—89° (after drying in air at room temperature) [Found: loss on drying at 100°, 6·4, 6·7. $C_{12}H_{22}ON_4,HCl,1{\cdot}5H_2O$ requires loss (for 1 H_2O), 6·0%] or 186—188° (after drying at 100°) (Found: C, 51·2; H, 8·4; N, 19·7; Cl′, 12·3. $C_{12}H_{22}ON_4,HCl,0{\cdot}5H_2O$ requires C, 50·8; H, 8·5; N, 19·75; Cl′, 12·5%).

4-Chloro-6-β-diethylaminoethylamino-2-methylpyrimidine (IX; R = H, R′ = Me, R″ = $[CH_2]_2{\cdot}NEt_2$).—4-β-Diethylaminoethylamino-6-hydroxy-2-methylpyrimidine hydrochloride (20 g.) and phosphoryl chloride (75 c.c.) were boiled under reflux for 3 hours. After removal of most of the excess of phosphoryl chloride under reduced pressure, the residue was poured on ice, and the solution made strongly alkaline with sodium hydroxide and extracted with chloroform. The chloroform solution was shaken several times with 5% acetic acid and the combined acetic acid extracts were treated with sodium hydroxide and shaken with chloroform. Evaporation of the dried (K_2CO_3) extract gave the *chloropyrimidine* as

a colourless oil (yield, 9·9 g.), b. p. 136—137°/0·15 mm. (Found : C, 54·0; H, 7·8. $C_{11}H_{19}N_4Cl$ requires C, 54·4; H, 7·8%). It gave a *dipicrate* which crystallised from methanol as yellow laminæ, m. p. 144—145° (Found : C, 39·7; H, 3·8; N, 20·1. $C_{11}H_{19}N_4Cl,2C_6H_3O_7N_3$ requires C, 39·4; H, 3·6; N, 20·0%).

4-Chloro-6-γ-diethylaminopropylamino-2-methylpyrimidine (IX; R = H R′ = Me, R″ = $[CH_2]_3{\cdot}NEt_2$), prepared similarly from 4-γ-diethylaminopropylamino-6-hydroxy-2-methylpyrimidine hydrochloride (dried at 100°) (17·5 g.) and phosphoryl chloride (75 c.c.), was obtained as a colourless oil (yield, 8·7 g.), b. p. 143—145°/0·15 mm. (Found : C, 55·9; H, 8·1; N, 21·7; Cl, 13·4. $C_{13}H_{23}N_4Cl$ requires C 56·1; H, 8·2; N, 21·8; Cl, 13·8%). The *dipicrate* crystallised from methanol in yellow laminæ, m. p. 158—159° (Found : C, 40·2; H, 3·6; N, 19·8. $C_{13}H_{21}N_4Cl,2C_6H_3O_7N_3$ requires C 40·3; H, 3·8; N, 19·6%).

Condensation of 4-Chloro-6-β-diethylaminoethylamino-2-methylpyrimidine with p-*Chloroaniline.*—A mixture of (IX; R = H, R′ = Me, R″ = $[CH_2]_2{\cdot}NEt_2$) (4·85 g.), *p*-chloroaniline (2·55 g.), water (25 c.c.), and 10N-hydrochloric acid (2·2 c.c.) was refluxed for 6 hours. The cooled solution was treated with sodium hydroxide; the product then separated as an oil which soon solidified. The solid was collected and dissolved in 5% acetic acid, and the solution was treated with decolourising carbon and filtered. The product was then reprecipitated by the addition of sodium hydroxide, filtered off, dried, and crystallised from light petroleum (b. p. >120°) (yield, 86·2%); it had m. p. 148° undepressed on admixture with 4-*p*-chloroanilino-6-β-diethylaminoethylamino-2-methylpyrimidine (see Part VIII) (Found : C, 61·1; H, 7·0; N, 21·2; Cl, 10·3. Calc. for $C_{17}H_{24}N_5Cl$: C, 61·3; H, 7·2; N, 21·0; Cl, 10·5%).

Condensation of 4-Chloro-6-γ-diethylaminopropylamino-2-methylpyrimidine with p-*Chloroaniline.*—4-Chloro-6-γ-diethylaminopropylamino-2-methylpyrimidine (5·1 g.), *p*-chloroaniline (2·55 g.), water (25 c.c.), and 10N-hydrochloric acid (2·2 c.c.) were boiled under reflux for 2 hours, and the solution was cooled and made alkaline with sodium hydroxide. The precipitated oil, isolated with chloroform, was extracted with 5% acetic acid. Basification (with sodium hydroxide) of the clarified acetic acid solution and extraction with chloroform followed by evaporation of the dried solution gave the base which crystallised from light petroleum (b. p. >120°); it had m. p. 129—131° identical with 4-*p*-chloroanilino-6-γ-diethylaminopropylamino-2-methylpyrimidine made by the method of Part VIII (Found : C, 62·1; H, 7·5; N, 19·9. Calc. for $C_{18}H_{26}N_5Cl$: C, 62·2; H, 7·5; N, 20·1%).

4-Chloro-6-δ-diethylamino-α-methylbutylamino-2-methylpyrimidine (IX; R = H, R′ = Me, R″ = $CHMe{\cdot}[CH_2]_3{\cdot}NEt_2$).—4-Chloro-6-hydroxy-2-methylpyrimidine (28·9 g.) and δ-diethylamino-α-methylbutylamine (31·6 g.) were mixed and heated at 150—160° for 8 hours. To the cooled residue phosphoryl chloride (180 c.c.) was added, the mixture refluxed for 3 hours, excess of phosphoryl chloride removed under reduced pressure, and the residue poured on ice. The resulting solution was made alkaline with sodium hydroxide and extracted with chloroform. Evaporation of the dried (K_2CO_3) chloroform solution and distillation of the residual oil gave the *chloropyrimidine* (yield, 36·4 g.), b. p. 168—170°/0·125 mm. (Found : C, 59·2; H, 8·3; N, 19·5; Cl, 12·7. $C_{14}H_{25}N_4Cl$ requires C, 59·0; H, 8·8; N, 19·7; Cl, 12·5%). The *dipicrate* crystallised from alcohol–2-ethoxyethanol in small yellow laminæ, m. p. 171—173° (Found : C, 41·7; H, 4·2; N, 19·1. $C_{14}H_{25}N_4Cl,2C_6H_3O_7N_3$ requires C, 42·0; H, 4·2; N, 18·9%).

Condensation of 4-Chloro-6-δ-diethylamino-α-methylbutylamino-2-methylpyrimidine with p-*Chloroaniline.*—4-Chloro-6-δ-diethylamino-α-methylbutylamino-2-methylpyrimidine (5·7 g.), *p*-chloroaniline (2·55 g.), water (25 c.c.), and 10N-hydrochloric acid (2·2 c.c.) were refluxed for 2 hours, and the resulting solution was cooled and made alkaline with sodium hydroxide. The precipitated oil was collected and extracted with 5% acetic acid, and the acetic acid extract clarified with carbon, filtered, and added to excess of sodium hydroxide solution. The oily product was extracted with chloroform, and the solution dried and evaporated. Distillation of the residue gave 4-*p*-chloroanilino-6-δ-diethylamino-α-methylbutylamino-2-methylpyrimidine, b. p. 220—225°/0·15 mm., identified as its *dipicrate*, m. p. 159—161° (Found : C, 46·2; H, 4·3; N, 18·2. $C_{20}H_{30}N_5Cl,2C_6H_3O_7N_3$ requires C, 46·1; H, 4·3; N, 18·5%). In Part VIII (*loc. cit.*) the m. p. of this picrate is given as 149—151°. The discrepancy is thought to be due to dimorphism, since repeat preparations of this picrate sometimes gave m. p. 149—151°, sometimes 159—161°, and sometimes intermediately. The exact conditions of crystallisation to obtain the two forms were not fully elucidated, but a preparation of the picrate from base made according to the method of Part VIII which had m. p. 159—161° (Found : C, 45·9; H, 4·3; N, 18·6%) showed no depression with the picrate described above.

4-Amino-2-p-chloroanilino-6-methylpyrimidine (II; R = H).—(*a*) 2-Chloro-4-amino-6-methylpyrimidine (7·2 g.), *p*-chloroaniline (6·4 g.), water (25 c.c.), and 10N-hydrochloric acid (0·5 c.c.) were refluxed for 1 hour. A clear solution was obtained after a few minutes refluxing, and the product then gradually separated. The mixture was diluted with water and made alkaline with ammonia, and the solid collected. The solid was dissolved in alcohol, and the solution made alkaline with ammonia and poured into water. The precipitated product was extracted with chloroform, and the solution dried (Na_2SO_4) and evaporated. Crystallisation of the residue from benzene–light petroleum gave colourless needles, m. p. 121—123°.

(*b*) 4-Chloro-2-*p*-chloroanilino-6-methylpyrimidine (10 g.) and aqueous ammonia (30 c.c.) were heated in a sealed tube at 140—150° for 12 hours. The contents of the tube were diluted with water and extracted with chloroform. Evaporation of the dried chloroform extract gave an oil which was purified by vacuum distillation (b. p. 190—192°/0·5 mm.). Crystallisation from benzene–light petroleum gave *4-amino-2-p-chloroanilino-6-methylpyrimidine*, m. p. 121—122° undepressed in admixture with material made by method (*a*) (Found : C, 56·7; H, 4·5; Cl, 15·1. $C_{11}H_{11}N_4Cl$ requires C, 56·3; H, 4·7; Cl, 15·1%) (4394).

2-Amino-4-p-chloroanilino-6-methylpyrimidine (III; R = H).—4-Chloro-2-amino-6-methylpyrimidine (7·2 g.), *p*-chloroaniline (6·4 g.), water (25 c.c.), and 10N-hydrochloric acid (0·5 c.c.) were refluxed for 1 hour. The reaction mixture was cooled, diluted with water, and made alkaline with ammonia. The precipitated product was filtered off, washed with water, and crystallised from aqueous alcohol, giving *2-amino-4-p-chloroanilino-6-methylpyrimidine* as colourless needles, m. p. 216—218° (Found : Cl, 15·2. $C_{11}H_{11}N_4Cl$ requires Cl, 15·1%) (4618).

Reaction of 4-*Chloro*-2-p-*chlorophenylguanidino*-6-*methylpyrimidine with Ammonia* (Experiment by Dr. P. A. Barrett).—4-Chloro-2-*p*-chlorophenylguanidino-6-methylpyrimidine (5 g.) and saturated alcoholic ammonia (25 c.c.) were heated in a sealed tube at 175° for 12 hours. The contents of the tube were evaporated to dryness and the residue was stirred with water. The resulting solid on fractional crystallisation from dilute alcohol gave 2-amino-4-*p*-chloroanilino-6-methylpyrimidine, m. p. and mixed m. p. 216—218° (Found: C, 56·2; H, 4·4; N, 23·7; Cl, 15·4. Calc. for $C_{11}H_{11}N_4Cl$: C, 56·3; H, 4·7; N, 23·9; Cl, 15·1%), as the less soluble fraction and *p*-chloroaniline as the more soluble.

4-*Amino*-6-p-*chloroanilino*-2-*methylpyrimidine* (I; R = H).—4-Chloro-6-amino-2-methylpyrimidine (7·2 g.), *p*-chloroaniline (6·4 g.), water (25 c.c.), and 10N-hydrochloric acid (0·5 c.c.) were refluxed for 1 hour. The reaction mixture was diluted with water and made alkaline with ammonia, and the product filtered off. The product was dissolved in alcohol, and the solution made alkaline with ammonia and poured into water. The precipitated product was filtered off and crystallised from aqueous alcohol, giving the *pyrimidine* as colourless flat prisms, m. p. 192—194° (Found: C, 56·4; H, 4·6; Cl, 15·2. $C_{11}H_{11}N_4Cl$ requires C, 56·3; H, 4·7; Cl, 15·1%).

4-*Chloro*-6-p-*chloroanilino*-2: 5-*dimethylpyrimidine* (V; R = Cl, R′ = R″ = Me).—(*a*) 4: 6-Dichloro-2: 5-dimethylpyrimidine (8·85 g.) (Huber and Hölscher, *Ber.*, 1938, **71**, 87), *p*-chloroaniline (6·4 g.), water (40 c.c.), acetone (20 c.c.), and 10N-hydrochloric acid (2 c.c.) were refluxed for 2 hours. The resulting solution was diluted with water and ammonia added to give an alkaline reaction to Brilliant-yellow. The precipitated *base* was filtered off, dissolved in alcohol with the addition of a little ammonia, and poured into water. The solid was collected, washed with water, dried, and crystallised from alcohol, giving colourless thick prisms (9 g.), m. p. 176—177° (Found: C, 54·1; H, 3·9; N, 16·2; Cl, 26·2. $C_{12}H_{11}N_3Cl_2$ requires C, 53·7; H, 4·1; N, 15·7; Cl, 26·5%).

(*b*) 4: 6-Dichloro-2: 5-dimethylpyrimidine (5·3 g.) and *p*-chloroaniline (4·2 g.) were heated in acetic acid (30 c.c.), containing a crystal of potassium iodide, at 40° for 20 hours. Addition of sodium acetate (4 g.) and dilution with water gave 4-chloro-6-*p*-chloroanilino-2: 5-dimethylpyrimidine which was filtered off, washed with water, and dried. It had m. p. and mixed m. p. 176° after crystallisation from benzene–light petroleum (Found: Cl, 26·5%).

4-*Chloro*-6-*hydroxy*-2: 5-*dimethylpyrimidine* (VI; R = Me).—4: 6-Dichloro-2: 5-dimethylpyrimidine (25 g.), water (250 c.c.), and hydrochloric acid (100 c.c.) were boiled together under reflux for 1 hour (complete homogeneity was obtained after ½ hour). The solution was cooled, made alkaline with sodium hydroxide, and then acidified with acetic acid. The precipitated *product* was filtered off and purified by dissolution in ammonia and reprecipitation with acetic acid. After drying, it crystallised from alcohol in colourless slender prisms (yield 16·3 g.), m. p. 225° (Found: C, 45·5; H, 4·4; N, 17·5; Cl, 22·8. $C_6H_7ON_3Cl$ requires C, 45·4; H, 4·4; N, 17·7; Cl, 22·4%).

4-*Chloro*-6-β-*diethylaminoethylamino*-2: 5-*dimethylpyrimidine* (IX; R = R′ = Me, R″ = $[CH_2]_2$·NEt_2).—4-Chloro-6-hydroxy-2: 5-dimethylpyrimidine (25 g.) and β-diethylaminoethylamine (18·3 g.) were mixed and heated at 150—160° for 8 hours. A portion of the resulting solid, on treatment with excess of picric acid in methanol solution, gave 4-β-*diethylaminoethylamino*-6-*hydroxy*-2: 5-*dimethylpyrimidine dipicrate* which crystallised from alcohol in yellow rectangular prisms, m. p. 154° (Found: C, 41·6; H, 4·2; N, 20·2. $C_{12}H_{22}ON_4,2C_6H_3O_7N_3$ requires C, 41·4; H, 4·0; N, 20·1%). The remainder of the hydrochloride was refluxed with phosphoryl chloride (220 c.c.) for 5 hours and the excess of phosphoryl chloride then removed by distillation under reduced pressure and the residue poured on ice. Addition of sodium hydroxide to the solution liberated the chloro-compound which was extracted with chloroform, and the extract was dried and evaporated. The residue was distilled in a vacuum giving 4-*chloro*-6-β-*diethylaminoethylamino*-2: 5-*dimethylpyrimidine* (21·9 g.), b. p. 139°/0·085 mm. (Found: C, 56·1; H, 8·2; Cl, 13·5. $C_{12}H_{21}N_4Cl$ requires C, 56·1; H, 8·2; Cl, 13·8%). It formed a *hydrate* which crystallised from light petroleum (b. p. 60—80°) in colourless thick laminæ, m. p. 80° (Found: C, 52·6; H, 8·4; N, 20·3. $C_{12}H_{21}N_4Cl,H_2O$ requires C, 52·5; H, 8·4; N, 20·4%), and a *dipicrate* which separated from alcohol in yellow laminæ, m. p. 143° (Found: N, 19·5. $C_{12}H_{21}N_4Cl,2C_6H_3O_7N_3$ requires N, 19·6%).

4-δ-*Diethylamino*-α-*methylbutylamino*-6-*hydroxy*-2: 5-*dimethylpyrimidine* (VIII; R = Me, R′ = CHMe·$[CH_2]_3$·NEt_2).—4-Chloro-6-hydroxy-2: 5-dimethylpyrimidine (31·7 g.) and δ-diethylamino-α-methylbutylamine (31·6 g.) were mixed and heated at 150—160° for 8 hours with stirring to give, on cooling, a viscous mass of 4-δ-diethylamino-α-methylbutylamino-6-hydroxy-2-methylpyrimidine hydrochloride which could not be crystallised. The *dipicrate*, prepared from the hydrochloride with excess of picric acid in methanol, crystallised from alcohol; m. p. 163—164° (Found: C, 43·9; H, 4·8. $C_{15}H_{23}ON_4,2C_6H_3O_7N_3$ requires C, 43·9; H, 4·6%).

4-*Chloro*-6-δ-*diethylamino*-α-*methylbutylamino*-2: 5-*dimethylpyrimidine* (IX; R = R′ = Me, R″ = CHMe·$[CH_2]_3$·NEt_2).—Phosphoryl chloride (225 c.c.) was added to the above crude hydrochloride (62 g.) and the mixture boiled under reflux for 4 hours. Most of the excess of phosphoryl chloride was removed under diminished pressure, the residue poured on ice, and, after solution had occurred, sodium hydroxide added to alkalinity, the oily product extracted with chloroform, and the extract dried and evaporated. Distillation of the residue gave the *chloropyrimidine* as a colourless oil (yield, 22·05 g.), b. p. 144—145°/0·055 mm. (Found: Cl, 12·1, 12·3. $C_{15}H_{27}N_4Cl$ requires Cl, 11·9%). A crystalline derivative was not obtained.

4-p-*Chloroanilino*-6-β-*diethylaminoethylamino*-2: 5-*dimethylpyrimidine* (IV; R = Cl, R′ = R″ = Me, R‴ = $[CH_2]_2$·NEt_2).—(*a*) 4-Chloro-6-*p*-chloroanilino-2: 5-dimethylpyrimidine (14·6 g.), β-diethylaminoethylamine (15 g.), and a crystal of potassium iodide were heated at 150—160° for 6 hours with stirring. The resulting melt was dissolved in dilute hydrochloric acid, and the solution made alkaline with sodium hydroxide and extracted with chloroform. After removal of the solvent the residue was stirred with 5% acetic acid, and the extract separated, stirred with decolourising carbon, and filtered. The filtrate was then made strongly alkaline with sodium hydroxide and extracted with chloroform, and the extract dried and evaporated. Distillation of the residual oil afforded 4-p-*chloroanilino*-6-β-*diethylaminoethylamino*-2: 5-*dimethylpyrimidine* as a colourless oil (yield, 11·6 g.), b. p. 200°/0·07 mm. (Found: C, 61·6; H, 7·5; N, 19·7; Cl, 10·2. $C_{18}H_{26}N_5Cl$ required C, 62·2; H, 7·5; N, 20·1; Cl, 10·2%). The base was converted into its *dihydrochloride* by dissolving in 2N-hydrochloric acid and

evaporating the solution to dryness. The residue was dried and freed from adhering hydrochloric acid by dissolving in alcohol and evaporation to dryness under reduced pressure several times. Crystallisation from alcohol–ethyl acetate then gave thin colourless prisms, m. p. 263—264° (Found: C, 51·0; H, 6·4; N, 16·4; Cl′, 16·2. $C_{18}H_{26}N_5Cl,2HCl$ requires C, 51·4; H, 6·7; N, 16·65; Cl′, 16·9%) (3990).

(*b*) A mixture of 4-chloro-6-β-diethylaminoethylamino-2 : 5-dimethylpyrimidine (5·13 g.), *p*-chloroaniline hydrochloride (3·28 g.), and hydrochloric acid (0·25 c.c.) was heated at 150—160° for 6 hours. By direct crystallisation of the resulting solid melt from alcohol–ethyl acetate, 4-*p*-chloroanilino-6-β-diethylaminoethylamino-2 : 5-dimethylpyrimidine dihydrochloride was obtained (yield, 5·7 g.), m. p. and mixed m. p. 262—264° (Found: C, 51·2; H, 6·1; N, 16·4; Cl′, 16·5%).

4-p-*Chloroanilino*-6-γ-*diethylaminopropylamino*-2 : 5-*dimethylpyrimidine* (IV; R = Cl, R′ = R″ = Me, R‴ = $[CH_2]_3$·NEt_2), prepared by method (*a*) above from 4-chloro-6-*p*-chloroanilino-2 : 5-dimethylpyrimidine and γ-diethylaminopropylamine, formed a colourless viscous oil, b. p. 204°/0·045 mm. (Found: C, 62·9; H, 7·8; N, 18·8; Cl, 9·8. $C_{19}H_{28}N_5Cl$ requires C, 63·1; H, 7·7; N, 19·4; Cl, 9·8%) which gave a *dihydrochloride* as colourless prisms from alcohol–ethyl acetate, m. p. 217—218° (Found: C, 48·8; H, 7·1; N, 14·9; Cl′, 15·1. $C_{19}H_{28}N_5Cl,2HCl,2H_2O$ requires C, 48·5; H, 7·2; N, 14·9; Cl′, 15·1%) (5507).

4-p-*Chloroanilino*-6-γ-*dimethylaminopropylamino*-2 : 5-*dimethylpyrimidine* (IV; R = Cl, R′ = R″ = Me, R‴ = $[CH_2]_3$·NMe_2), prepared in a corresponding manner using γ-dimethylaminopropylamine, was obtained as colourless prisms from light petroleum (b. p. 60—80°), m. p. 105° (Found: C, 61·2; H, 7·0; N, 20·6. $C_{17}H_{24}N_5Cl$ requires C, 61·2; H, 7·2; N, 21·0%). It gave a *dihydrochloride* which crystallised from alcohol–ethyl acetate in tiny colourless prisms, m. p. 275—276° (decomp.) (the m. p. varied slightly with the rate of heating) (Found: C, 49·9; H, 6·3; N, 17·3; Cl′, 17·2. $C_{17}H_{24}N_5Cl,2HCl$ requires C, 50·2; H, 6·4; N, 17·2; Cl′, 17·5%) (4067).

4-p-*Chloroanilino*-6-δ-*diethylamino*-α-*methylbutylamino*-2 : 5-*dimethylpyrimidine* (IV; R = Cl, R′ = R″ = Me, R‴ = CHMe·$[CH_2]_3$·NEt_2).—The condensate (150—160° for 6 hours) of 4-chloro-6-δ-diethylamino-α-methylbutylamino-2 : 5-dimethylpyrimidine (14·93 g.) and *p*-chloroaniline (8·2 g.) was dissolved in dilute hydrochloric acid, made alkaline with sodium hydroxide, and then extracted with chloroform. Evaporation of the dried chloroform extract and distillation of the residue gave the *base* (9·4 g.) as a colourless highly viscous oil, b. p. 208°/0·55 mm. (Found: C, 64·5; H, 7·8; Cl, 9·5. $C_{21}H_{33}N_5Cl$ requires C, 64·7; H, 8·2; Cl, 9·1%) (3988). No solid salt could be isolated.

4-p-*Bromoanilino*-6-β-*diethylaminoethylamino*-2 : 5-*dimethylpyrimidine* (IV; R = Br, R′ = R″ = Me, R‴ = $[CH_2]_2$·NEt_2).—4-Chloro-6-β-diethylaminoethylamino-2 : 5-dimethylpyrimidine (10·26 g.) was mixed with *p*-bromoaniline hydrochloride (6·9 g.), a few drops of hydrochloric acid were added, and the whole was heated at 150—160° for 6 hours. The melt, originally fluid, was completely solid after 2·5 hours. Crystallisation from alcohol–ethyl acetate gave the *dihydrochloride* as colourless thick prisms, m. p. 265—266° (Found: C, 46·3; H, 6·4. $C_{18}H_{26}N_5Br,2HCl$ requires C, 46·45; H, 6·0%).

4-*Chloro*-6-p-*anisidino*-2 : 5-*dimethylpyrimidine* (V; R = Cl, R′ = OMe, R″ = Me).—(*a*) 4 : 6-Dichloro-2 : 5-dimethylpyrimidine (8·85 g.), *p*-anisidine (6·15 g.), water (40 c.c.), acetone (20 c.c.), and 10N-hydrochloric acid (1 c.c.) were refluxed for 3 hours. The mixture was diluted with water and made alkaline with ammonia. The filtered product was dissolved in 2-ethoxyethanol, and the solution made alkaline by the addition of a little ammonia and then poured into water. The precipitated solid was collected, washed with water, and dried. Crystallised from *n*-propanol, the *base* (9·5 g.) had m. p. 201° (Found: C, 58·8; H, 5·0; N, 15·8; Cl, 13·1. $C_{13}H_{14}ON_3Cl$ requires C, 59·2; H, 5·3; N, 15·9; Cl, 13·5%).

(*b*) 4 : 6-Dichloro-2 : 5-dimethylpyrimidine (5·31 g.), *p*-anisidine (4·5 g.), glacial acetic acid (30 c.c.), and 10N-hydrochloric acid (0·2 c.c.) were stirred at 40—45° for 20 hours. Sodium acetate (4 g.) was then added and the solution diluted with water (300 c.c.). On standing, the product gradually separated and was filtered off, washed with water, and dried. Crystallisation from benzene gave 4-chloro-6-*p*-anisidino-2 : 5-dimethylpyrimidine (6·4 g.) as colourless needles, m. p. and mixed m. p. 201° (Found: Cl, 13·4%).

4-p-*Anisidino*-6-β-*diethylaminoethylamino*-2 : 5-*dimethylpyrimidine* (IV; R = OMe, R′ = R″ = Me, R‴ = $[CH_2]_2$·NEt_2).—The above chloropyrimidine (10 g.), β-diethylaminoethylamine (14 g.), and a crystal of potassium iodide were heated at 150—160° for 6 hours with stirring. The resulting reaction mixture was worked up as described previously for the corresponding *p*-chloroanilino-compound and gave the *base* (8·9 g.) as a colourless viscous oil, b. p. 203°/0·5 mm. (Found: C, 67·0; H, 9·3; N, 19·8. $C_{19}H_{29}ON_5$ requires C, 66·5; H, 8·5; N, 20·4%). The *dihydrochloride* crystallised from alcohol–ethyl acetate in clusters of colourless prisms, m. p. 254—255° (Found: C, 52·5; H, 7·7; N, 16·1; Cl′, 16·9. $C_{19}H_{29}ON_5,2HCl,H_2O$ requires C, 52·5; H, 7·6; N, 16·1; Cl′, 16·4%) (3962).

4-*Chloro*-6-p-*nitroanilino*-2 : 5-*dimethylpyrimidine* (V; R = NO_2, R′ = R″ = Me).—4 : 6-Dichloro-2 : 5-dimethylpyrimidine (5·22 g.), *p*-nitroaniline (4·55 g.), acetic acid (50 c.c.), and a crystal of potassium iodide were heated at 55—60° for 18 hours. Sodium acetate (3 g.) was then added and the solution diluted with water (500 c.c.). The precipitated solid was filtered off, washed with water, and dried. Crystallised from butanol, the *base* formed yellow prisms (yield, 5·2 g.), m. p. 208—210° (Found: Cl, 12·9; $C_{12}H_{11}O_2N_4Cl$ requires Cl, 12·7%).

4-p-*Nitroanilino*-6-β-*diethylaminoethylamino*-2 : 5-*dimethylpyrimidine* (IV; R = NO_2, R′ = R″ = Me, R‴ = $[CH_2]_2$·NEt_2).—(*a*) An intimate mixture of 4-chloro-6-β-diethylaminoethylamino-2 : 5-dimethylpyrimidine (1·0 g.) and *p*-nitroaniline hydrochloride (0·68 g.) was heated at 150—160° for 6 hours with stirring in the initial stages. The cold melt was dissolved in hydrochloric acid, and the solution made alkaline with sodium hydroxide and extracted with chloroform. The chloroform solution was then extracted several times with 5% acetic acid and the combined acetic acid extracts were added to excess of sodium hydroxide. The precipitated oil was taken up in chloroform, and the solution dried and evaporated. Crystallisation of the residue from light petroleum (b. p. 80—100°) gave the *base* as thick yellow laminæ, m. p. 104—106° (Found: C, 60·4; H, 7·3, N, 23·1. $C_{18}H_{26}O_2N_6$ requires C, 60·3; H, 7·3; N, 23·5%).

(*b*) 4-Chloro-6-*p*-nitroanilino-5 : 6-dimethylpyrimidine (1·8 g.), β-diethylaminoethylamine (1·8 g.),

and a trace of potassium iodide were heated at 155—165° for 5 hours and the mixture was worked up in the same way as in (*a*) to give the base (1·8 g.) which was converted into its *dihydrochloride*. This crystallised from alcohol–ethyl acetate in yellowish rectangular prisms, m. p. 254—256° (Found: C, 50·1; H, 6·5; N, 19·4. $C_{18}H_{26}O_3N_6,2HCl$ requires C, 50·1; H, 6·5; N, 19·5%) (4188).

4 : 6-*Dichloro*-2-*methyl*-5-*ethylpyrimidine*.—4 : 6-Dihydroxy-2-methyl-5-ethylpyrimidine (30 g.) (Ferris and Ronzio, *J. Amer. Chem. Soc.*, 1940, **62**, 606) and phosphoryl chloride (110 c.c.) were refluxed for 2 hours and the bulk of the excess of phosphoryl chloride was then removed under diminished pressure. The residue was poured on ice (200 g.), the product extracted with benzene, and the solution dried (Na_2SO_4). The benzene was then removed by distillation through a short fractionating column and the residue distilled giving 4 : 6-*dichloro*-2-*methyl*-5-*ethylpyrimidine* as a colourless oil, b. p. 212—214° (Found: Cl, 37·2. $C_7H_8N_2Cl_2$ requires Cl, 37·2%).

4-*Chloro*-6-*hydroxy*-2-*methyl*-5-*ethylpyrimidine* (VI; R = Et).—4 : 6-Dichloro-2-methyl-5-ethylpyrimidine (25 g.), water (250 c.c.), and hydrochloric acid (100 c.c.) were boiled under reflux for 2·5 hours. The resulting clear solution was cooled, made alkaline with ammonia, and then acidified with acetic acid. Next day the product was filtered off and purified by dissolution in dilute sodium hydroxide and reprecipitation with acetic acid. The dried *base* crystallised from alcohol in colourless elongated prisms (yield, 19·2 g.), m. p. 209° (Found: C, 49·0; H, 5·0; N, 16·4. $C_7H_9ON_2Cl$ requires C, 48·7; H, 5·2; N, 16·2%).

4-p-*Chloroanilino*-6-*hydroxy*-2-*methyl*-5-*ethylpyrimidine* (VII; R = Cl, R′ = Et).—4-Chloro-6-hydroxy-2-methyl-5-ethylpyrimidine (8·63 g.), *p*-chloroaniline (9·6 g.), and hydrochloric acid (0·5 c.c.) were mixed and heated at 160—170° for 8 hours. After cooling, the melt was dissolved in warm aqueous sodium hydroxide, and the solution treated with decolourising carbon and filtered. Addition of acetic acid to the filtrate gave the product which was filtered off, digested with aqueous ammonia, collected, and dried. 4-p-*Chloroanilino*-6-*hydroxy*-2-*methyl*-5-*ethylpyrimidine* crystallised from 2-ethoxyethanol in colourless needles (yield, 8·1 g.), m. p. 275° (Found: C, 59·0; H, 5·9; N, 16·1. $C_{13}H_{14}ON_3Cl$ requires C, 59·2; H, 6·1; N, 15·9%).

4-*Chloro*-6-p-*chloroanilino*-2-*methyl*-5-*ethylpyrimidine* (V; R = Cl, R′ = Et, R″ = Me).—(*a*) 4 : 6-Dichloro-2-methyl-5-ethylpyrimidine (5·73 g.) and *p*-chloroaniline (4·3 g.) were dissolved in acetic acid (30 c.c.), a crystal of potassium iodide was added, and the solution was stirred at 35—45° for 20 hours. Sodium acetate (3 g.) was then added and the solution drowned into water to precipitate the *base* which was filtered off, dried, and crystallised, first from benzene–light petroleum (b. p. 60—80°) and then from dilute alcohol; long colourless rectangular prisms, m. p. 166° (Found: C, 55·6; H, 4·4; N, 14·5; Cl, 25·2. $C_{13}H_{13}N_3Cl_2$ requires C, 55·3; H, 4·6; N, 15·0; Cl, 25·2%).

(*b*) 4-*p*-Chloroanilino-6-hydroxy-2-methyl-5-ethylpyrimidine (8·9 g.) and phosphoryl chloride (45 c.c.) were refluxed for 1½ hours, and the clear solution was cooled and poured on ice. After being stirred for ½ hour the solution was made alkaline with sodium hydroxide and the precipitated product filtered off, washed with water, and dried. On boiling it with benzene a small amount of unchanged hydroxy-compound remained undissolved. This was removed by filtration and the benzene evaporated. Crystallisation of the residue from dilute alcohol gave the same compound as in (*a*), m. p. and mixed m. p. 166° (Found: C, 55·6; H, 4·4; N, 14·8%).

4-*γ*-*Diethylaminopropylamino*-6-*hydroxy*-2-*methyl*-5-*ethylpyrimidine* (VIII; R = Et, R′ = $[CH_2]_3{\cdot}NEt_2$).—4-Chloro-6-hydroxy-2-methyl-5-ethylpyrimidine (34·5 g.) and γ-diethylaminopropylamine (26 g.) were heated at 150—160° for 8 hours, with stirring until the melt solidified. A small sample of the resulting hydrochloride of 4-γ-diethylaminopropylamino-6-hydroxy-2-methyl-5-ethylpyrimidine on treatment with picric acid in alcohol gave the *dipicrate* which crystallised from 2-ethoxyethanol–alcohol in flat yellow prisms, m. p. 188° (Found: C, 42·9; H, 4·7; N, 19·4. $C_{14}H_{24}ON_4,2C_6H_3O_7N_3$ requires C, 43·1; H, 4·4; N, 19·3%).

4-*Chloro*-6-*γ*-*diethylaminopropylamino*-2-*methyl*-5-*ethylpyrimidine* (IX; R = Et, R′ = Me, R″ = $[CH_2]_3{\cdot}NEt_2$).—The above hydrochloride (59·5 g.) was refluxed with phosphoryl chloride (225 c.c.) during 15 hours, and the reaction mixture worked up as described previously for this type of compound, giving the *chloropyrimidine* as a colourless oil, b. p. 142°/0·095 mm. (Found: N, 19·1; Cl, 12·1. $C_{14}H_{23}N_4Cl$ requires N, 19·7; Cl, 12·5%). It gave a *dipicrate* which crystallised from alcohol in yellow tables, m. p. 147—148° (Found: C, 42·0; H, 4·2; N, 18·8. $C_{14}H_{23}N_4Cl,2C_6H_3O_7N_3$ requires C, 42·0; H, 4·2; N, 18·85%).

4-p-*Chloroanilino*-6-*β*-*diethylaminoethylamino*-2-*methyl*-5-*ethylpyrimidine* (IV; R = Cl, R′ = Et, R″ = Me, R‴ = $[CH_2]_2{\cdot}NEt_2$).—4-Chloro-6-*p*-chloroanilino-2-methyl-5-ethylpyrimidine (2·0 g.), β-diethylaminoethylamine (2·0 g.), and a crystal of potassium iodide were stirred and heated at 140—150° for 6 hours. The resulting mixture was dissolved in dilute hydrochloric acid and the solution made alkaline with sodium hydroxide. The precipitate was separated by decantation and dissolved in 5% acetic acid, and the solution was filtered. On addition of sodium hydroxide to the filtrate, the base was obtained as an oil which was extracted with benzene, and the extract was dried and evaporated. The residual oily base gave a *dihydrochloride* which crystallised from alcohol–ethyl acetate in colourless thick prisms, m. p. 268—270° (decomp.) (Found: C, 52·3; H, 6·8; N, 16·0; Cl′, 16·3. $C_{19}H_{28}N_5Cl,2HCl$ requires C, 52·5; H, 6·9; N, 16·1; Cl′, 16·3%) (4046).

4-p-*Chloroanilino*-6-*γ*-*dimethylaminopropylamino*-2-*methyl*-5-*ethylpyrimidine* (IV; R = Cl, R′ = Et, R″ = Me, R‴ = $[CH_2]_3{\cdot}NMe_2$).—Obtained similarly from 4-chloro-6-*p*-chloroanilino-2-methyl-5-ethylpyrimidine and γ-dimethylaminopropylamine, this gave a *dipicrate* which crystallised from alcohol in thick yellow laminæ, m. p. 171—173° (Found: C, 45·1; H, 4·5. $C_{19}H_{28}N_5Cl,2C_6H_3O_7N_3$ requires C, 44·7; H, 4·0%), and a *dihydrochloride* which crystallised from alcohol–ethyl acetate in colourless flat prisms, m. p. 278—279° (decomp.) (Found: C, 47·7; H, 7·3; N, 15·1; Cl′, 15·3. $C_{19}H_{28}N_5Cl,2HCl,2H_2O$ requires C, 47·3; H, 7·0; N, 15·3; Cl′, 15·6%) (4017).

4-p-*Chloroanilino*-6-*γ*-*diethylaminopropylamino*-2-*methyl*-5-*ethylpyrimidine* (IV; R = Cl, R′ = Et, R″ = Me, R‴ = $[CH_2]_3{\cdot}NEt_2$).—4-Chloro-6-γ-diethylaminopropylamino-2-methyl-5-ethylpyrimidine (8·35 g.), *p*-chloroaniline (4·8 g.), and a few drops of hydrochloric acid were heated at 150—160° for 6 hours with stirring. The melt (cooled) was dissolved out with hydrochloric acid and the solution

made alkaline with sodium hydroxide. The liberated oil was extracted with benzene, and the extract dried and evaporated. Distillation of the remaining oil gave 4-p-*chloroanilino*-6-*γ-diethylaminopropylamino*-2-*methyl*-5-*ethylpyrimidine* (6·3 g.), b. p. 210°/0·065 mm. (Found: C, 63·5; H, 8·0. $C_{20}H_{30}N_5Cl$ requires C, 63·9; H, 8·0%), which formed a *dihydrochloride*, colourless prisms from alcohol–ethyl acetate, m. p. 162° (Found: C, 50·9; H, 7·1; N, 14·9; Cl′, 14·8. $C_{20}H_{30}N_5Cl,2HCl,H_2O$ requires C, 51·4; H, 7·3; N, 15·0; Cl′, 15·2%).

4-p-*Anisidino*-6-*hydroxy*-2-*methyl*-5-*ethylpyrimidine* (VII; R = OMe, R′ = Et).—4-Chloro-6-hydroxy-2-methyl-5-ethylpyrimidine (17·25 g.), *p*-anisidine (12·3 g.), and hydrochloric acid (1 c.c.) were heated at 160—170° for 3 hours. The mixture was dissolved in dilute sodium hydroxide solution, and the solution treated with decolourising carbon and filtered. Acidification of the filtrate with acetic acid gave a product which was freed from a small amount of unchanged 4-chloro-6-hydroxy-2-methyl-5-ethylpyrimidine by stirring with 10% aqueous ammonia for 3 hours and filtering. After being washed with water and dried, the *base* crystallised from alcohol in colourless thick prisms, m. p. 199—200° (Found: C, 65·0; H, 6·6; N, 16·3. $C_{14}H_{17}O_2N_3$ requires C, 64·9; H, 6·6; N, 16·2%).

4-*Chloro*-6-p-*anisidino*-2-*methyl*-5-*ethylpyrimidine* (V; R = OMe, R′ = Et, R″ = Me).—(*a*) 4 : 6-Dichloro-2-methyl-5-ethylpyrimidine (5·73 g.) and *p*-anisidine (4·1 g.) were kept in acetic acid (30 c.c.), with the addition of a crystal of potassium iodide, at 40—45° for 20 hours. After addition of sodium acetate (3 g.) the solution was drowned into water (300 c.c.), and the precipitated *product* filtered off, washed with water, and crystallised from dilute alcohol; colourless elongated prisms, m. p. 157° (Found: C, 60·6; H, 5·7; N, 15·2. $C_{14}H_{16}ON_2Cl$ requires C, 60·5; H, 5·8; N, 15·1%).

(*b*) 4-*p*-Anisidino-6-hydroxy-2-methyl-5-ethylpyrimidine (11·9 g.) and phosphoryl chloride (60 c.c.) were boiled under reflux for 1½ hours and the clear solution poured on ice. Addition of ammonia precipitated the product which was purified by crystallisation from dilute alcohol. It then had m. p. 157° either alone or in admixture with material made by method (*a*) (Found: C, 60·1; H, 5·4%).

4-p-*Anisidino*-6-*β-diethylaminoethylamino*-2-*methyl*-5-*ethylpyrimidine* (IV; R = OMe, R′ = Et, R″ = Me, R‴ = $[CH_2]_2{\cdot}NEt_2$).—4-Chloro-6-*p*-anisidino-2-methyl-5-ethylpyrimidine (2·75 g.) and *β*-diethylaminoethylamine (2·5 g.) were heated at 155—165° for 8 hours and the mixture worked up as in the case of the corresponding *p*-chloroanilino-compound, giving the *dihydrochloride* as colourless laminæ from alcohol–ethyl acetate, m. p. 250—251° (decomp.) (Found: C, 55·5; H, 7·5; N, 15·9; Cl′, 16·3. $C_{20}H_{31}ON_5,2HCl$ requires C, 55·8; H, 7·7; N, 16·3; Cl′, 16·5%) (4048).

4-p-*Anisidino*-6-*γ-dimethylaminopropylamino*-2-*methyl*-5-*ethylpyrimidine* (IV; R = OMe, R′ = Et, R″ = Me, R‴ = $[CH_2]_3{\cdot}NMe_2$).—4-Chloro-6-*p*-anisidino-2-methyl-5-ethylpyrimidine (2·75 g.) and *γ*-dimethylaminopropylamine (2·5 g.) were heated, with the addition of a trace of potassium iodide, at 150—160° for 8 hours with stirring. The melt was dissolved in dilute hydrochloric acid and the solution poured into excess of sodium hydroxide solution. The precipitated product was collected and purified by dissolution in 5% acetic acid and reprecipitation with sodium hydroxide. The *base*, isolated by extraction with benzene, crystallised from light petroleum (b. p. 80—100°) in colourless needles, m. p. 106—107° (Found: C, 66·2; H, 7·8; N, 20·3. $C_{19}H_{29}ON_5$ requires C, 66·5; H, 8·5; N, 20·4%) (4069).

4 : 6-*Dichloro*-5-*phenyl*-2-*methylpyrimidine*.—4 : 6-Dihydroxy-5-phenyl-2-methylpyrimidine (40 g.) (Dox and Yoder, *J. Amer. Chem. Soc.*, 1922, **44**, 361) and phosphoryl chloride (140 c.c.) were boiled under reflux for 2 hours. The excess of phosphoryl chloride was then removed under reduced pressure and the residue poured on a mixture of ice and water (300 g.). After ½ hour's stirring, the *product* which had separated was filtered off, washed acid-free with water, and crystallised from alcohol; colourless plates, m. p. 160° (Found: C, 55·2; H, 3·1; Cl, 29·1. $C_{11}H_8N_2Cl_2$ requires C, 55·2; H, 3·35; Cl, 29·7%).

4-*Chloro*-6-p-*chloroanilino*-5-*phenyl*-2-*methylpyrimidine* (V; R = Cl, R′ = Ph, R″ = Me).—4 : 6-Dichloro-5-phenyl-2-methylpyrimidine (11·95 g.) and *p*-chloroaniline (6·4 g.) were ground together, acetic acid (3 g.) was added, and the mixture was heated at 110—115° for 1 hour. The cooled melt was dissolved in alcohol, and the solution made alkaline with ammonia and poured into water. The precipitated *base* was filtered off, washed with water, and dried. Crystallised from light petroleum (b. p. >120°), it formed colourless prisms (9·5 g.), m. p. 155—156° (Found: C, 62·1; H, 4·1; N, 12·8; Cl, 21·2. $C_{17}H_{13}N_3Cl_2$ requires C, 61·8; H, 3·9; N, 12·7; Cl, 21·5%).

4-p-*Chloroanilino*-6-*β-diethylaminoethylamino*-5-*phenyl*-2-*methylpyrimidine* (IV; R = Cl, R′ = Ph, R″ = Me, R‴ = $[CH_2]_2{\cdot}NEt_2$).—The above chloropyrimidine (12·0 g.), *β*-diethylaminoethylamine (12·0 g.), and a crystal of potassium iodide were heated at 150—160° for 6 hours with stirring and then worked up to give the *pyrimidine* which crystallised from light petroleum (b. p. 40—60°) in colourless laminæ, m. p. 88—89° (Found: C, 67·0; H, 7·1; N, 17·5. $C_{23}H_{28}N_5Cl$ requires C, 67·4; H, 6·8; N, 17·1%).

4-p-*Chloroanilino*-6-*γ-diethylaminopropylamino*-5-*phenyl*-2-*methylpyrimidine* (IV; R = Cl, R′ = Ph, R″ = Me, R‴ = $[CH_2]_3{\cdot}NEt_2$), prepared in a similar manner using *γ*-diethylaminopropylamine in place of *β*-diethylaminoethylamine, crystallised from light petroleum (b. p. 40—60°) in colourless thick rectangular prisms, m. p. 77—78° (Found: C, 67·7; H, 6·8; N, 16·7. $C_{24}H_{30}N_5Cl$ requires C, 68·0; H, 7·1; N, 16·5%). A crystalline dihydrochloride could not be obtained either from this or the preceding compound.

4-*Chloro*-2-*amino*-6-p-*chloroanilinopyrimidine* (V; R = Cl, R′ = H, R″ = NH_2).—(*a*) 4 : 6-Dichloro-2-aminopyrimidine (12·3 g.) and *p*-chloroaniline (9·6 g.) were ground together, acetic acid (9·0 g.) was added, and the mixture was heated to 110°. After a few minutes at this temperature a vigorous reaction occurred, and the reaction mixture which had previously become fluid and homogeneous suddenly set solid. The cooled and ground melt was boiled with alcohol (150 c.c.) containing ammonia for 1½ hours, then diluted with water, and the *product* collected and dried. Crystallised from ethyl acetate it formed colourless prisms (yield, 11·6 g.), m. p. 242—243° (Found: C, 47·1; H, 3·2; N, 21·9; Cl, 28·1. $C_{10}H_8N_4Cl_2$ requires C, 47·1; H, 3·1; N, 22·0; Cl, 27·7%). Addition of hydrochloric acid to its alcoholic solution gave a *hydrochloride* as colourless needles, m. p. 252—254° (Found: N, 18·2; Cl, 33·6. $C_{10}H_8N_4Cl_2,HCl,H_2O$ requires N, 18·1; Cl, 34·4%).

(*b*) 4 : 6-Dichloro-2-aminopyrimidine (8·2 g.), *p*-chloroaniline (6·3 g.), water (40 c.c.), acetone (10 c.c.),

and 10N-hydrochloric acid (0·5 c.c.) were boiled under reflux for 2 hours. After cooling, the product was filtered off, washed with water, and dissolved in boiling 2-ethoxyethanol with the addition of ammonia to give an alkaline reaction. After dilution with water the precipitated product was filtered off, washed with water, dried, and crystallised from ethyl acetate; m. p. 241—242° either alone or admixed with the product from (*a*) above (yield, 6·5 g.).

4-*Chloro*-2-*amino*-6-p-*anisidinopyrimidine* (V; R = OMe, R′ = H, R″ = NH_2).—To an intimate mixture of 4 : 6-dichloro-2-aminopyrimidine (12·3 g.) and *p*-anisidine (9·2 g.), acetic acid (4·5 g.) was added and the mixture heated to 110°; a vigorous reaction then took place. After ½ hour at 110°, the melt was cooled, ground, and stirred with dilute ammonia for 2 hours. The resulting *base* was filtered off, washed with water, and crystallised from alcohol, giving colourless prisms (8·9 g.), m. p. 224—225° (Found: C, 53·1; H, 4·6; N, 22·1. $C_{11}H_{11}ON_4Cl$ requires C, 52·7; H, 4·4; N, 22·35%). The *hydrochloride* had m. p. 236° (decomp.) (Found: N, 19·3; Cl, 24·1. $C_{11}H_{11}ON_4Cl,HCl$ requires N, 19·5; Cl, 24·7%).

4-*Chloro*-2-*amino*-6-p-*toluidinopyrimidine* (V; R = Me, R′ = H, R″ = NH_2), prepared similarly using *p*-toluidine in place of *p*-anisidine, crystallised from alcohol in colourless laminæ, m. p. 239—241° (Found: C, 56·1; H, 4·7; N, 23·8. $C_{11}H_{11}N_4Cl$ requires C, 56·3; H, 4·7; N, 23·9%). It formed a *hydrochloride*, m. p. 259—260° (decomp.) (Found: N, 20·3; Cl, 26·4. $C_{11}H_{11}N_4Cl,HCl$ requires N, 20·3; Cl, 26·4%).

2-*Amino*-4-p-*chloroanilino*-6-*β*-*diethylaminoethylaminopyrimidine* (IV; R = Cl, R′ = H, R″ = NH_2, R‴ = $[CH_2]_2{\cdot}NEt_2$).—(*a*) 4-Chloro-2-amino-6-*p*-chloroanilinopyrimidine hydrochloride (9·7 g.) and *β*-diethylaminoethylamine (4·84 g.) were heated at 150—160° for 5 hours, and the mixture was cooled and dissolved in water. To the solution sodium hydroxide was added, and the precipitated product was extracted with chloroform. The chloroform solution was shaken several times with 5% acetic acid and the acid extracts were combined, made alkaline with sodium hydroxide, and extracted with chloroform. The dried chloroform solution, on evaporation, gave the *base* which crystallised from benzene in colourless laminæ (8 g.), m. p. 135° (Found: C, 57·4; H, 7·0; N, 24·7. $C_{16}H_{23}N_6Cl$ requires C, 57·4; H, 6·9; N, 25·1%) (3861).

(*b*) 4-Chloro-2-amino-6-*β*-diethylaminoethylaminopyridimine (6·1 g.) (see below) and *p*-chloroaniline hydrochloride (4·1 g.) were mixed and heated in an oil-bath at 170—180° for 6 hours. The resulting melt was dissolved in warm dilute hydrochloric acid and then worked up as in (*a*) to give 2-amino-4-*p*-chloroanilino-6-*β*-diethylaminoethylaminopyrimidine, m. p. and mixed m. p. 134—135°.

By method (*a*) above a number of other 2-*amino*-4-*arylamino*-6-*dialkylaminoalkylaminopyrimidines* were prepared. Details of these are given in Table I.

4-*Chloro*-2-*amino*-6-p-*chloroanilino*-5-*ethylpyrimidine* (V; R = Cl, R′ = Et, R″ = NH_2).—4 : 6-Dichloro-2-amino-5-ethylpyrimidine (19·2 g.) (v. Merkatz, *Ber.*, 1919, **52**, 869) and *p*-chloroaniline (12·75 g.) were ground together, acetic acid (6 g.) was added, and the mixture was heated at 100—110° for ½ hour with stirring. A homogeneous melt was obtained which suddenly solidified after about ½ hour. The cooled and ground melt was dissolved in boiling alcohol with the addition of ammonia to give an alkaline reaction, and the solution poured into water. The precipitated *product* was filtered off and dried. By crystallisation from benzene it was obtained as colourless tables (19·25 g.), m. p. 158—160° (Found: C, 51·2; H, 4·2; N, 19·4. $C_{12}H_{12}N_4Cl_2$ requires C, 50·9; H, 4·2; N, 19·8%). The *hydrochloride* crystallised from alcohol containing a little hydrochloric acid in long colourless prisms, m. p. >290° (Found: C, 45·6; H, 4·5; N, 17·6. $C_{12}H_{12}N_4Cl_2,HCl$ requires C, 45·1; H, 4·1; N, 17·5%).

4-*Chloro*-2-*amino*-6-p-*cyanoanilino*-5-*ethylpyrimidine* (V; R = CN, R′ = Et, R″ = NH_2).—4 : 6-Dichloro-2-amino-5-ethylpyrimidine (12·8 g.) and *p*-cyanoaniline (7·86 g.) were mixed, and acetic acid (4 g.) was added. After being heated for some time at 120° the fluid mixture suddenly solidified. Heating at 120—130° was continued for 1 hour, and the melt then dissolved in 2-ethoxyethanol, ammonia added, and the solution poured into water. The dried precipitated *product* crystallised from butanol in colourless rhombs (10 g.), m. p. 230—232° (Found: C, 57·0; H, 4·1; N, 25·1. $C_{13}H_{12}N_5Cl$ requires C, 57·0; H, 4·4; N, 25·6%).

4 : 6-*Dichloro*-2-*amino*-5-*phenylpyrimidine*.—Guanidine nitrate (24·4 g.) was added to a hot solution of sodium (9·2 g.) in methanol (250 c.c.) and, after ½ hour's refluxing, ethyl phenylmalonate (47·2 g.) was added. The mixture was boiled under reflux for 3 hours and then allowed to cool. The solid was collected and the filtrate evaporated; the residue and the solid were combined and dissolved in warm water, and the solution was treated with decolourising carbon and filtered. The filtrate was acidified with acetic acid at 80°, and the product collected, washed with water, and dried (25·6 g.). This 2-amino-4 : 6-dihydroxy-5-phenylpyrimidine (20 g.) and phosphoryl chloride (90 c.c.) were boiled under reflux for 3 hours, and the resulting clear solution was poured on ice (600 g.) with stirring. After 2 hours' stirring, ammonia was gradually added until the mixture was neutral. The solid product was filtered off, washed with water, and dried. Purification by vacuum sublimation at 160—170°/14 mm. followed by crystallisation from alcohol, gave 4 : 6-*dichloro*-2-*amino*-5-*phenylpyrimidine* as colourless plates, m. p. 221—222° (Found: C, 50·3; H, 2·9; N, 17·3. $C_{10}H_7N_3Cl_2$ requires C, 50·0; H, 2·9; N, 17·5%).

4-*Chloro*-2-*amino*-6-p-*chloroanilino*-5-*phenylpyrimidine* (V; R = Cl, R′ = Ph, R″ = NH_2).—Acetic acid (3 g.) was added to an intimate mixture of 4 : 6-dichloro-2-amino-5-phenylpyrimidine (12·0 g.) and *p*-chloroaniline (6·45 g.) and the whole heated at 120—130° for 1·5 hours. The mixture gradually melted and then resolidified. After being ground and stirred with dilute ammonia, the solid product was dissolved in 2-ethoxyethanol, ammonia added to alkalinity, and the solution diluted with water. The crystalline *pyrimidine* which separated on standing was filtered off, dried, and crystallised from butanol; colourless laminæ, m. p. 228—229° (Found: C, 58·0; H, 3·6; N, 16·6. $C_{16}H_{12}N_4Cl_2$ requires C, 58·0; H, 3·6; N, 16·9%).

2-*Amino*-4-*arylamino*-6-*dialkylaminoalkylamino*-5-*substituted Pyrimidines*.—The appropriate 4-chloro-2-amino-6-arylaminopyrimidine was heated with excess of dialkylaminoalkylamine and a trace of potassium iodide for 6 hours at 160—165°. The resulting mixture was dissolved in dilute hydrochloric acid and the solution filtered, if necessary, from insoluble material. The filtrate was added to excess

TABLE I.

TABLE I.

2-Amino-4-arylamino-6-dialkylaminoalkylaminopyrimidines.

Ref. No.	Substituent at 4.	Substituent at 6.	Solvent; appearance.	M. p.	Formula.	Analysis. Found, %.	Analysis. Required, %.
3925	C_6H_4Cl (*p*)	$[CH_2]_2{\cdot}NMe_2$	Benzene	139—140°	$C_{14}H_{19}N_6Cl$	C, 55·1; H, 6·4; N, 26·8	C, 54·8; H, 6·2; N, 27·4
3939	C_6H_4Cl (*p*)	$[CH_2]_3{\cdot}NEt_2$	Benzene–light petroleum (b. p. 60—80°); prisms	109—111	$C_{17}H_{23}N_6Cl$	C, 59·0; H, 7·7; N, 23·9	C, 58·5; H, 7·2; N, 24·1
3923	C_6H_4Cl (*p*)	$[CH_2]_3{\cdot}NMe_2$	Benzene; plates	132—134	$C_{15}H_{21}N_6Cl$	C, 56·4; H, 6·6; N, 25·7	C, 56·2; H, 6·6; N, 26·2
3934	C_6H_4Cl (*p*)	$CHMe{\cdot}[CH_2]_3{\cdot}NEt_2$	Benzene–light petroleum (b. p. 60—80°); prisms	128—130	$C_{19}H_{29}N_6Cl$	C, 60·9; H, 7·9; N, 21·8	C, 60·5; H, 7·7; N, 22·3
3913	$C_6H_4{\cdot}OMe$ (*p*)	$[CH_2]_2{\cdot}NEt_2$	Benzene; plates	123—125	$C_{17}H_{26}ON_6$	C, 62·3; H, 7·5; N, 25·4	C, 61·8; H, 7·9; N, 25·45
3922	$C_6H_4{\cdot}Me$ (*p*)	$[CH_2]_2{\cdot}NEt_2$	Benzene–light petroleum (b. p. 60—80°); tables	108—109	$C_{17}H_{26}N_6$	C, 65·0; H, 8·8; N, 26·2	C, 65·0; H, 8·3; N, 26·8

TABLE II.

2-Amino-4-p-chloroanilino-6-dialkylaminoalkylamino-5-substituted Pyrimidines.

Ref. No.	Substituent at 5.	Substituent at 6.	Solvent.	M. p.	Formula.	Analysis. Found, %.	Analysis. Required, %.
4072	Et	$[CH_2]_2{\cdot}NEt_2$	Light petroleum (b. p. 60—80°)	71—72°	$C_{16}H_{27}N_6Cl$	analysis sample lost	
4109	Et	$[CH_2]_3{\cdot}NEt_2$	Light petroleum (b. p. 80—100°)	102—103	$C_{19}H_{29}N_6Cl$	C, 60·6; H, 7·5; N, 22·3	C, 60·5; H, 7·7; N, 22·3
4108	Et	$[CH_2]_3{\cdot}NMe_2$	Light petroleum (b. p. 100—120°)	130—132	$C_{17}H_{25}N_6Cl$	C, 58·8; H, 7·1; N, 24·0	C, 58·5; H, 7·2; N, 24·1
*	Et	$[CH_2]_2{\cdot}NEt_2$	Benzene	151—152	$C_{19}H_{27}N_7$	C, 64·1; H, 7·6; N, 27·3	C, 64·6; H, 7·6; N, 27·8
4133	Ph	$[CH_2]_3{\cdot}NEt_2$	Alcohol	170—171	$C_{23}H_{27}N_6Cl$	C, 64·5; H, 6·4; N, 20·0	C, 64·3; H, 6·6; N, 20·4
4199	Ph	$[CH_2]_3{\cdot}NMe_2$	Alcohol	157—158	$C_{21}H_{25}N_6Cl$	C, 63·9; H, 6·4; N, 20·5	C, 63·6; H, 6·3; N, 21·2
4200	Ph	$[CH_2]_3{\cdot}NEt_2$	Alcohol	172—173	$C_{23}H_{29}N_6Cl$	C, 64·6; H, 6·5; N, 20·4	C, 65·0; H, 6·8; N, 19·8

All these compounds formed colourless laminæ, except the last two which were obtained as colourless thick prisms. * 4-*p*-Cyanoanilino-compound.

TABLE III.

4-Chloro-2-amino-6-aminoalkylaminopyrimidines.

Ref. No.	Substituent at 5.	Substituent at 6.	Solvent.	M. p.	Formula.	Analysis. Found, %.	Analysis. Required, %.
4284	H	$[CH_2]_2{\cdot}NEt_2$	Benzene–light petroleum (b. p. 60—80°) [1]	93—95°	$C_{10}H_{18}N_5Cl$	C, 49·6; H, 7·0; N, 28·4	C, 49·3; H, 7·4; N, 28·7
4552	H	$[CH_2]_3{\cdot}NEt_2$	Light petroleum (b. p. 100—120°) [2]	86—87	$C_{11}H_{20}N_5Cl$	C, 51·5; H, 7·8; N, 26·8	C, 51·3; H, 7·8; N, 27·2
4395	Et	$[CH_2]_2{\cdot}NEt_2$	Benzene–light petroleum (b. p. 60—80°) [2]	105—106	$C_{12}H_{22}N_5Cl$	C, 53·2; H, 7·6; N, 25·2	C, 53·4; H, 8·1; N, 25·8
4442	Et	$[CH_2]_3{\cdot}NEt_2$	Benzene [2]	115—116	$C_{13}H_{24}N_5Cl$	C, 54·4; H, 8·6	C, 54·6; H, 8·4
4441	Et	$[CH_2]_3{\cdot}N<[CH_2]_4>CH_2$	Toluene [2]	170—171	$C_{14}H_{24}N_5Cl$	C, 56·9; H, 8·2	C, 56·8; H, 8·1
4395	Ph	$[CH_2]_2{\cdot}NEt_2$	Benzene–light petroleum (b. p. 60—80°) [3]	138—139	$C_{16}H_{22}N_5Cl$	C, 59·6; H, 6·8; N, 21·7	C, 60·1; H, 6·9; N, 21·9
4320	Ph	$[CH_2]_3{\cdot}NEt_2$	Benzene–light petroleum (b. p. 60—80°) [3]	131—132	$C_{17}H_{24}N_5Cl$	C, 61·2; H, 6·7; N, 21·0	C, 61·2; H, 7·2; N, 21·0
4415	Ph	$[CH_2]_3{\cdot}N<[CH_2]_4>CH_2$	Benzene [3]	151—152	$C_{18}H_{24}N_5Cl$	C, 62·5; H, 6·4; N, 19·6	C, 62·5; H, 6·9; N, 20·3

[1] Colourless flat needles. [2] Colourless laminæ. [3] Colourless prisms.

of sodium hydroxide and the precipitated product either filtered off or (if liquid) extracted with chloroform. In either case purification was effected by extraction with 5% acetic acid and reprecipitation with sodium hydroxide. The precipitated product was collected and dried, or extracted with chloroform and the dried extract evaporated, and then crystallised. The *compounds* prepared are given in Table II.

4-*Chloro*-2-*amino*-6-*aminoalkylaminopyrimidines*.—The requisite 4 : 6-dichloro-2-aminopyrimidine was mixed with the aminoalkylamine (1 mol.) and acetic acid (1 mol.), and heated at 100—110° (115—120° in the case of the 5-phenyl compounds) for 3 hours. The cooled mixture was lixiviated with dilute hydrochloric acid and the solution filtered from unchanged pyrimidine. Addition of sodium hydroxide to the filtrate precipitated the product which was isolated either by filtration or by extraction with ether and then purified by dissolution in 5% acetic acid and reprecipitation with sodium hydroxide. If solid, the product was filtered off and dried; otherwise, it was extracted with ether, and the solution dried and evaporated. The product was then crystallised. Details of the *compounds* prepared are given in Table III.

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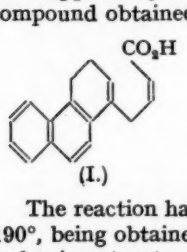
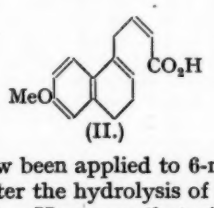
252. γ-6-*Methoxy*-1 : 2 : 3 : 4-*tetrahydro*-1-*naphthylidenecrotonic Acid*.

By WALTER C. J. ROSS.

γ-6-*Methoxy*-1 : 2 : 3 : 4-*tetrahydro*-1-*naphthylidenecrotonic acid* has been prepared and its structure elucidated by oxidative degradation and by measurement of its ultra-violet absorption spectrum. The acid can be used in a convenient new synthesis of 1-keto-7-methoxy-1 : 2 : 3 : 4-tetrahydrophenanthrene.

IT has been shown that γ-bromocrotonic esters can be used in the Reformatsky reaction in the same way as α-bromo-esters (Fuson, Arnold, and Cooke, *J. Amer. Chem. Soc.*, 1938, **60**, 2272; Ziegler, Schumann, and Winkelmann, *Annalen*, 1942, **551**, 120) and this method has recently been applied by Cook and Schoental (*J.*, 1945, 288), who suggested the formula (I) for the compound obtained from 1-keto-1 : 2 : 3 : 4-tetrahydrophenanthrene.


(I.)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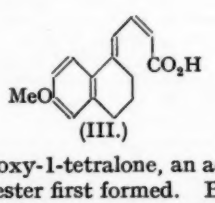
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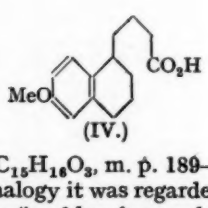
(IV.)

The reaction has now been applied to 6-methoxy-1-tetralone, an acid, $C_{15}H_{16}O_3$, m. p. 189—190°, being obtained after the hydrolysis of the ester first formed. By analogy it was regarded as having structure (II). However, the acid exhibits absorption maxima (in chloroform solution) at 2490 A. and 3480 A., $\varepsilon = 10{,}300$ and 30,000 respectively. These figures are in much better agreement with a structure such as (III), since this contains a more extended system of conjugation, though the wave-length of the primary maximum is rather higher than would be expected for even this system—this fact could possibly be ascribed to the " exocyclicity " of one of the double bonds. Structure (III) is also supported by the fact that when the acid is oxidised by alkaline potassium permanganate an 80% yield of 6-methoxy-1-tetralone is obtained. Rearrangement of the double bonds is very unlikely under the mild conditions of the oxidation and so the new acid is regarded as γ-6-*methoxy*-1 : 2 : 3 : 4-*tetrahydro*-1-*naphthylidenecrotonic acid* (III).

When the acid is heated at 280—300° with palladium-black, a 55% yield of γ-6-methoxy-1-naphthylbutyric acid is obtained. If the *methyl* ester of (III) is similarly heated and the product is hydrolysed, an almost quantitative yield of the naphthalenic acid is obtained. Cyclisation of the acid thus formed yields 1-keto-7-methoxy-1 : 2 : 3 : 4-tetrahydrophenanthrene (Bachmann, Cole, and Wilds, *J. Amer. Chem. Soc.*, 1940, **62**, 284) which is a useful intermediate in the production of synthetic hormones, particularly those of the doisynolic acid series (Heer, Billeter, and Miescher, *Helv. Chim. Acta*, 1945, **28**, 1342); the method now described is a very convenient one for the preparation of this ketone.

Reduction of the acid (III) in acetic acid–ethanol solution using a palladium catalyst, or in aqueous alkaline solution using a Raney nickel catalyst, gives a high yield of γ-6-methoxy-1 : 2 : 3 : 4-tetrahydro-1-naphthylbutyric acid (IV), and when heated with sulphur at 200° this is converted into γ-6-methoxy-1-naphthylbutyric acid (compare Haberland, *Ber.*, 1936 **69**, 1380). These reactions provide an alternative route for the conversion of the acid (III) into 1-keto-7-methoxy-1 : 2 : 3 : 4-tetrahydrophenanthrene.

EXPERIMENTAL.

(M. ps. were determined in sealed capillaries and are uncorrected.)

γ-6-Methoxy-1 : 2 : 3 : 4-tetrahydro-1-naphthylidenecrotonic Acid (III).—Zinc wool (35 g.) was placed in a large flask, dry benzene (400 c.c.) containing mercuric chloride (100 mg.) added, and the mixture warmed for 15 minutes. 6-Methoxy-1-tetralone (94 g.) was added and then ethyl γ-bromocrotonate (114 g., b. p. 80—85°/2 mm., prepared essentially by the method of Ziegler *et al.*, *Annalen*, 1942, **551**, 80) was run in at such a rate that the reaction proceeded at a vigorous but controllable pace. The mixture was heated under reflux for a further hour after all the ester had been added, and by this time a deep red complex had separated and most of the zinc had dissolved. The mixture was cooled and decomposed by shaking it with 2N-hydrochloric acid (500 c.c.). The product was extracted with ether, and the extract was washed with water, evaporated, and heated under reflux for 2 hours with potassium hydroxide (50 g.) in methanol (500 c.c.) and water (100 c.c.). The mixture was diluted with water and extracted with ether—this extract contained unchanged ketone (50 g.)—and then the aqueous layer was acidified, a yellow precipitate of the unsaturated *acid* being formed. The solid (28 g.) was collected and recrystallised from acetone or methanol; it formed hard prisms, m. p. 189—190° (Found: C, 73·2; H, 6·8. $C_{15}H_{16}O_3$ requires C, 73·7; H, 6·6%).

The *methyl* ester was prepared by the action of an ethereal solution of diazomethane on the acid or by refluxing the acid (10 g.) with methanol (80 c.c.) containing acetyl chloride (10 c.c.) for one hour (compare Riegel and Moffat, *J. Amer. Chem. Soc.*, 1943, **65**, 1971). In each case the crystalline residue obtained after evaporating off the solvents was recrystallised from methanol, giving lemon-yellow prismatic plates of the ester, m. p. 85—86° (Found: C, 74·2; H, 7·2. $C_{16}H_{18}O_3$ requires C, 74·4; H, 7·0%).

Oxidation of Acid (III).—The acid (2 g.) was dissolved in excess of 2N-sodium carbonate, and finely powdered potassium permanganate was added to the stirred solution until the supernatant liquid remained coloured. The product was extracted with ether, and the extract dried (Na_2SO_4) and evaporated. 6-Methoxy-1-tetralone (1·15 g., 80%), m. p. 78—79° (undepressed by admixture with an authentic specimen of m. p. 79°), was obtained.

γ-6-Methoxy-1-naphthylbutyric Acid.—The methyl ester of (III) (10 g.) was heated at 280—300° for 1 hour in a metal-bath with palladium-black (700 mg.). The product was dissolved in methanol (60 c.c.), potassium hydroxide (10 g. in 10 c.c. of water) added, and the mixture heated under reflux for 2 hours. The cooled solution was filtered and then acidified with dilute hydrochloric acid; the naphthalenic acid (9·7 g.), m. p. 149—151°, was thus precipitated (Cohen, Cook, and Hewett, *J.*, 1936, 52, give m. p. 150—151°).

Reduction of Acid (III).—(*a*) The acid (1·0 g.) was dissolved in ethanol (75 c.c.) and acetic acid (10 c.c.), and after addition of palladium–strontium carbonate (500 mg. containing 5% palladium) the solution was shaken in an atmosphere of hydrogen. Hydrogen was rapidly absorbed, and after ½ hour the theoretical volume of gas (calculated for the reduction of two double bonds) had been taken up. The solvents were evaporated, and the oily residue was crystallised from light petroleum (b. p. 60—80°), giving the required acid, m. p. 76—78° (900 mg.) (Haberland, *loc. cit.*, gives m. p. 79°).

(*b*) The acid (2·5 g.) was dissolved in water (25 c.c.) containing sodium hydroxide (6 c.c. 2N), Raney nickel catalyst (1 g.) added, and the mixture shaken in an atmosphere of hydrogen. The theoretical volume of hydrogen was absorbed in 3 hours. After filtration, the solution was acidified, and the oily precipitate crystallised from light petroleum. In this way 2·1 g. of the required acid, m. p. 77°, were obtained.

When the acid prepared by either method was heated at 200° for 3 hours with ½ its weight of sulphur, γ-6-methoxy-1-naphthylbutyric acid, m. p. 149—150°, was obtained.

The author's thanks are due to Professor J. W. Cook, F.R.S., for suggesting this method of preparing 1-keto-7-methoxy-1 : 2 : 3 : 4-tetrahydrophenanthrene, to Dr. E. A. Braude for measuring the absorption spectrum, and to Organon Laboratories Ltd. for permission to publish the results.

RESEARCH DEPT. ORGANON LABORATORIES LTD.,
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253. *The Structure of Anhydrotetronic Acid.*

By D. H. MARRIAN, P. B. RUSSELL, A. R. TODD, and W. S. WARING.

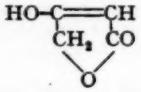
Anhydrotetronic acid, obtained by refluxing tetronic acid in aqueous solution, is shown by degradative studies to have structure (II).

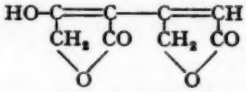
IN the course of investigations in this laboratory on the hatching factor for the potato eelworm (*Heterodera rostochiensis* Wollenweber) produced by certain host species of *Solanaceæ* it was observed that anhydrotetronic acid possessed the property of hatching eelworm cysts (Calam, Todd, and Waring, to be published elsewhere). Since this acid was at that time the only active synthetic substance known, it was a matter of considerable importance for further work that its precise structure should be ascertained, and the investigation described in this paper was accordingly carried out.

Anhydrotetronic acid was first described by Wolff and Schwabe (*Annalen*, 1896, **291**, 251), who obtained it as colourless crystals containing one molecule of water of crystallisation by heat,

ing an aqueous solution of tetronic acid (I). The anhydrous acid, $C_8H_8O_5$, was monobasic and had m. p. 263° (decomp.). Later Wolff (*Annalen*, 1901, **315**, 162) showed that it contained in all probability a reactive methylene group, since with aliphatic and aromatic aldehydes it gave alkylidene- or arylidene-bisanhydrotetronic acids; analogous compounds are obtained from tetronic acid on similar treatment. No further examination of anhydrotetronic acid seems to have been made.

Anhydrotetronic acid, like tetronic acid, owes its acidic properties to an enolic hydroxyl group; it gives a maroon colour with ferric chloride and couples readily with diazonium compounds. On treatment with diazomethane it gives a neutral *methyl ether* giving no ferric reaction, and on bromination it yields a *mono-bromo*-derivative. It shows strong selective light absorption in the ultra-violet region, and hydrolytic titration at 100° with N/100-sodium hydroxide shows only 20% of the uptake expected for one lactone group. Under optimum conditions anhydrotetronic acid is formed in a yield of only *ca.* 33% by heating aqueous solutions of tetronic acid, but when the water is replaced by aqueous morpholine reaction proceeds rapidly and the yield is almost quantitative. These facts suggest that anhydrotetronic acid has structure (II), but, especially since no analogous compound is obtained under similar conditions from either α- or γ-substituted tetronic acids, it was considered desirable to establish the validity of this structure by degradative methods.

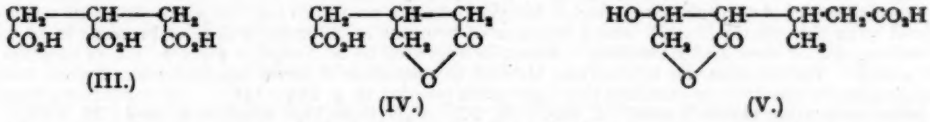
(I.) 

 (II.)

Oxidation of anhydrotetronic acid with potassium permanganate gave oxalic acid, while fusion with potassium hydroxide yielded both oxalic and acetic acids. Refluxed with dilute sulphuric acid, anhydrotetronic acid evolved 1 mol. of carbon dioxide during 15 hours; the product, a resinous acid, gave a crystalline p-*phenylphenacyl* ester, but was not identified. Hydrogenation of anhydrotetronic acid in methanolic solution with a platinum catalyst proceeded rather slowly and ceased when about 2·5 mols. of hydrogen had been taken up. The product was not homogeneous and could be readily separated into neutral and acidic fractions. The acidic fraction was semi-solid, and no crystalline derivative could be prepared from it. It clearly contained an enolic hydroxyl group, since it gave a maroon ferric reaction and showed selective light absorption at 2330 A. (ε, 5000). Titration of the crude fraction gave an equivalent of 221, and hydrolytic titration caused a further uptake of alkali equivalent to 93% of that required for a second acid grouping. The failure to isolate any crystalline derivative from the material suggested that it was probably a mixture of acids; it was accordingly oxidised with potassium permanganate in the hope of obtaining identifiable fragments which would give some clue to its nature. Oxidation was at first rapid but slowed down later and was stopped when the equivalent of 6 atoms of oxygen had been used up. From the product, tricarballylic acid (propane-1:2:3-tricarboxylic acid) (III) and homoparaconic acid (homopilosinic acid, butanolide-2-acetic acid) (IV) were isolated. The isolation of (IV) is significant, since it is clear that in its formation the portion of the anhydrotetronic acid molecule (and of the enolic reduced acid) containing the enolic hydroxyl group has been destroyed. The lactone ring of (IV) is derived from one of the tetronic acid residues present in the starting material, and it is evident that the β-carbon atom in this residue must have been joined to the α-position of the second (enolic) residue in anhydrotetronic acid.

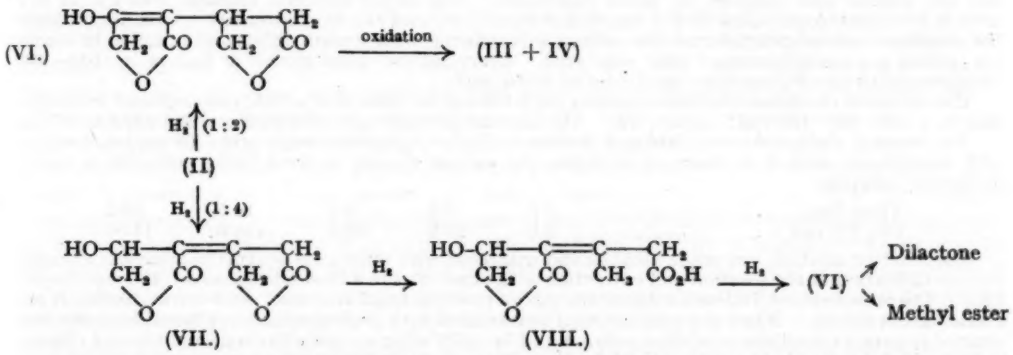
The distilled neutral fraction from the hydrogenation of anhydrotetronic acid was stable to permanganate and showed no selective light absorption in the ultra-violet region. It was evidently a mixture, since it gave analytical values lying between those corresponding to $C_8H_{10}O_4$ and $C_9H_{14}O_5$ and hydrolytic titration gave an equivalent of 101. Treatment with hydrazine gave a mixture of isomeric dihydrazides, $C_8H_{18}O_4N_4$, which was separated into one pure *dihydrazide*, m. p. 155°, which was sparingly soluble in methanol, and a mixture of more soluble dihydrazides, m. p. 125—140°. Both the dihydrazide, m. p. 155°, and the isomer mixture were oxidised by periodate, 3 mols. of reagent being consumed in each case. Since model experiments showed that hydrazides are oxidised by periodate according to the equation $2R{\cdot}CO{\cdot}NH{\cdot}NH_2 + 2O = R{\cdot}CO{\cdot}NH{\cdot}NH{\cdot}COR + N_2 + 2H_2O$, it can be deduced that the dihydrazides obtained above contain one α-glycol grouping. From these facts it is concluded that the neutral fraction from the hydrogenation contained the methyl ester of a lactonic hydroxy-acid, $C_9H_{12}O_4$, and the corresponding dilactone in their various stereoisomeric modifications; treatment of such a mixture with hydrazine would obviously yield a mixture of stereo-

isomeric dihydrazides. It may further be inferred that the potential carboxyl groups of the two tetronic acid molecules involved in the formation of anhydrotetronic acid are still present in the latter compound, and that the ring which has been opened by hydrogenolysis to form the acid $C_8H_{12}O_4$ is not the one bearing the enolic hydroxyl of anhydrotetronic acid. The acid $C_8H_{12}O_4$ is therefore regarded as a β-(2-hydroxybutanolide-1)-butyric acid (V).



(III.) (IV.) (V.)

These results suffice to establish beyond reasonable doubt structure (II) for anhydrotetronic acid. The course of the hydrogenation described above is explained on the basis of this structure according to the scheme given below. Addition of hydrogen in the 1 : 2-position of the conjugated system would give (VI), probably the major component of the acidic fraction, since as a substituted tetronic acid its further hydrogenation would be slow (Kumler, *J. Amer. Chem. Soc.*, 1938, **60**, 859); oxidation of (VI) would yield tricarballylic and homoparaconic acids. Addition of hydrogen in the 1 : 4-position would yield (VII) as initial product in which ready hydrogenolysis of one lactone ring would occur giving (VIII). Further hydrogenation of (VIII) would yield the lactonic acid (V), which either lactonises or is esterified by the solvent under the conditions of hydrogenation (cf. Waser, *Helv. Chim. Acta*, 1925, **8**, 117) giving the neutral fraction isolated.



The fact that α-substituted tetronic acids are recovered unchanged after treatment under conditions leading to the formation of anhydrotetronic acid (II) from tetronic acid is readily understood, but failure to prepare corresponding anhydro-acids from γ-substituted tetronic acids is rather surprising. On heating an aqueous solution of tetronic acid, the formation of anhydrotetronic acid can be followed by the rise in equivalent. Under similar conditions a definite, although smaller, rise in equivalent was observed with γ-methyltetronic acid (54% increase in 90 minutes) or γγ-dimethyltetronic acid (7% increase in 90 minutes), indicating that some condensation had occurred; no anhydro-acids could be isolated from the resulting solutions, nor could the starting material be recovered. Like α-acetyltetronic acid (Baker, Grice, and Jansen, *J.*, 1943, 241), anhydrotetronic acid ($pK = 1{\cdot}99$) is a much stronger acid than tetronic acid which has $pK = 3{\cdot}76$ (Kumler, *loc. cit.*), and as in the case of α-acetyltetronic acid this increase can be attributed to the increased resonance possibilities in the ionised form. Structural models show that substitution on the γ-carbon atom of tetronic acid would prevent the derived anhydro-acid from assuming a planar configuration, with consequent loss of resonance possibilities. As a result the derived anhydro-acid would be less stable and might decompose rapidly after formation or the condensation might take a different course after the initial aldol stage; either possibility would explain the experimental results.

Experimental.

Anhydrotetronic Acid.—(1) *In water.* Tetronic acid (5 g.) in water (15 c.c.) was refluxed for 10 minutes. On cooling, anhydrotetronic acid separated in small crystals (1·6 g.), m. p. 261°. Recrystallised from water it had m. p. 263° (decomp.).

(2) *In aqueous morpholine.* Tetronic acid (1·75 g.) in water (10 c.c.) and morpholine (1 c.c.) were refluxed for 10 minutes; the solution was cooled and acidified with sulphuric acid, giving 1·6 g. of

anhydrotetronic acid, m. p. 260° (decomp.). Recrystallised from water it had m. p. 263° (decomp.). Light absorption in alcohol: maxima at 3100 A. (ε, 14,200) and 2560 A. (ε, 9600).

Methyl Ether of Anhydrotetronic Acid.—Anhydrotetronic acid (200 mg.) in cold methanol (25 c.c.) was treated with excess of ethereal diazomethane. The solution was left overnight and then evaporated under reduced pressure, the residual oil was diluted with ether, and the brownish needles were collected and recrystallised from methanol (charcoal). The *ether* formed colourless plates, m. p. 185° (colours on heating) [Found: C, 55·0; H, 4·1; OMe, 16·1. $C_9H_8O_5$ requires C, 55·1; H, 4·1; OMe (1), 15·8%].

Bromination of Anhydrotetronic Acid.—Anhydrotetronic acid (100 mg.) in a few drops of water was covered with chloroform (2 c.c.), and a solution of bromine in chloroform (1 g. of bromine in 10 c.c. of chloroform) added slowly with shaking. Reaction appeared to be complete when 0·7 c.c. of solution had been added. The solution was filtered and allowed to evaporate at room temperature; a glass resulted which gradually solidified on standing to a hard white powder, m. p. 144—146°. Attempts to recrystallise the *bromo*-derivative failed (Found: C, 34·5; H, 2·7. $C_8H_5O_5Br,H_2O$ requires C, 34·4; H, 2·5%).

Oxidation of Anhydrotetronic Acid with Potassium Permanganate.—Anhydrotetronic acid (404 mg.) in water (20 c.c.) was treated with potassium permanaganate solution (1·5 g. in 100 c.c. of solution), of which 10 c.c. were taken up (*ca.* 5 atoms of oxygen). The solution was filtered and acidified with dilute sulphuric acid. Volatile acid corresponding to 8·5 c.c. of N/10-sodium hydroxide was removed by steam distillation. The residual solution was exhaustively extracted with ether, evaporation of which gave a yellow solid (340 mg.). Recrystallised from ether it gave colourless prisms, m. p. 102°; these were concluded to be oxalic acid from equivalent determination (Found: equiv., 64. Calc. for $C_2H_2O_4,2H_2O$: equiv., 63) and from the fact that they gave an insoluble calcium salt.

Potassium Hydroxide Fusion of Anhydrotetronic Acid.—Anhydrotetronic acid (250 mg.), potassium hydroxide (1 g.), and water (1 c.c.) were heated in a nickel crucible until fused. The melt was deep red at first but became yellow as the temperature was raised. When the temperature reached 250°, a further quantity (1 g.) of potassium hydroxide was added. The temperature was then raised to 300° and maintained for 10 minutes. The cooled melt was dissolved in water, acidified, and extracted with ether, evaporation of which left a brownish solid smelling of acetic acid. The residue was dissolved in water and the volatile acid removed by steam distillation. The steam distillate required 7·85 c.c. of N/10-sodium hydroxide (equivalent to 47·1 mg. of acetic acid; 0·7 mol.) for neutralisation. After neutralisation the distillate was evaporated and the sodium salt refluxed with *p*-phenylphenacyl bromide in alcohol. On cooling a *p*-phenylphenacyl ester separated. Recrystallised from alcohol it had m. p. 108—109°, undepressed by the *p*-phenylphenacyl ester of acetic acid.

Extraction of the steam distillation residue gave 126 mg. of oxalic acid which, recrystallised from ether, had m. p. 98—100° (Found: equiv., 62). The amount of oxalic acid obtained corresponded to 0·7 mol.

Treatment of Anhydrotetronic Acid with Sulphuric Acid.—Anhydrotetronic acid (508 mg.) was refluxed with N-sulphuric acid in a steam of nitrogen, the carbon dioxide evolved being collected in barium hydroxide solution.

Time (hrs.)	0·5	2·5	6·5	14·5	16·5
CO_2 (% mol.)	5·6	27·9	55·0	108·0	110·0

The reaction mixture was made alkaline and extracted with ether; no neutral fraction was obtained. On reacidification of the solution and extraction with ether it gave a brown resinous oil (400 mg.) (equiv., 135). The resin reduced Tollens's reagent and gave a positive Legal reaction; with ferric chloride it gave a weak green colour. When the acid (50 mg.) was treated with *p*-phenylphenacyl bromide in the usual manner it gave a colourless crystalline *ester*, m. p. 156—158° after recrystallisation from ethanol (Found: C, 75·3; H, 5·5. $C_{21}H_{18}O_4$ requires C, 75·4; H, 5·4%). Anhydrotetronic acid was recovered unchanged after being heated on the steam-bath for 2 hours with 2% oleum.

Hydrogenation of Anhydrotetronic Acid.—Anhydrotetronic acid (3 g.) in methanol (75 c.c.) was shaken with hydrogen in presence of platinum (from 0·25 g. of platinum oxide), 859 c.c. being absorbed in 4 hours. The catalyst was then removed and the methanol evaporated; water was added and the solution neutralised with N/10-sodium hydroxide and extracted continuously with ether for 24 hours. The ether was dried and removed, giving a neutral residue (0·9 g.), which distilled as a pale yellow viscous oil, b. p. 180—190° (bath temp.)/10^{-5} mm., stable to potassium permanganate in the cold [Found: C, 54·5; H, 6·6; OMe, 4·5; active H_2, 0·22; *M* (Rast), 210; equiv. by hydrolytic titration, 101, 98. Calc. for $C_9H_{14}O_5$: C, 53·5; H, 6·9; OMe (1), 15·3; active H_2 (1), 0·50%; *M*, 202; equiv. (2 potential CO_2H), 101. Calc. for $C_8H_{10}O_4$: C, 56·4; H, 5·9%; *M*, 170; equiv., 85]. Acidification of the alkaline solution followed by extraction with ether gave a semi-solid acid fraction (2 g.) (1st equiv., 221 in cold; 2nd equiv., 198 in warm. Calc. for $C_8H_8O_5$: 1st equiv., 184; 2nd equiv., 184). The substance was acid to Congo-red and was rapidly oxidised by permanganate in the cold. It was soluble in cold alkali and gave a maroon colour with ferric chloride. Light absorption in alcohol: maximum at 2330 A. (ε, 5000).

Hydrazides from Neutral Fraction from Hydrogenation.—The above neutral fraction (0·2 g.) was heated with hydrazine (1 g.) on a steam-bath for 3½ hours. Excess of hydrazine was removed under reduced pressure leaving a crystalline residue. Extraction with boiling methanol gave a crystalline almost insoluble *dihydrazide*, m. p. 155° (Found: C, 40·9; H, 7·5; N, 23·5. $C_8H_{18}O_4N_4$ requires C, 41·1; H, 7·7; N, 23·9%). The methanol extract was diluted with ethyl acetate and yielded a mixture of isomeric dihydrazides, m. p. 125—140° (Found: N, 23·9. Calc. for $C_8H_{18}O_4N_4$: N, 23·9%). The dihydrazide, m. p. 155° (13·4 mg.; $0·0573 \times 10^{-3}$ mol.), in water was treated with 1 c.c. of 0·235M-sodium periodate; $0·173 \times 10^{-3}$ mol. of periodate was absorbed (*i.e.*, 3·02 mols. of periodate per mol. of dihydrazide). The mixed dihydrazides (21·0 mg.) were treated with 2 c.c. of 0·235M-sodium periodate and used up 1·095 c.c. (*i.e.*, 2·89 mols. per mol.).

Oxidation of Benzhydrazide with Periodate.—Benzhydrazide (131·5 mg.; $0·968 \times 10^{-3}$ mol.) treated with 5 c.c. of 0·235M-periodate used up 4·05 c.c., *i.e.*, 0·982 mols. per mol. The solid which separated, recrystallised from aqueous methanol, had m. p. 238—239° alone or mixed with dibenzoylhydrazine, m. p. 239°.

Oxidation of the Acid Fraction from Hydrogenation.—The acid fraction (1·17 g.) from the above hydrogenation was dissolved in acetone (20 c.c.) and water (20 c.c.), and 2% potassium permanganate was added dropwise with stirring at room temperature. When 3 atoms of oxygen had been taken up the rate of oxidation slowed considerably; in all 6 atoms of oxygen were added. The solution was filtered, acidified, and extracted with ether. On standing, crystalline material separated from the ether, m. p. 157—159°, undepressed in admixture with authentic tricarballylic acid (m. p. 158—159°). The solution was evaporated, giving an oil which subsequently crystallised and then had m. p. 70—73°. Recrystallised from chloroform–carbon disulphide it had m. p. 78°. Sublimation in a vacuum (70°/10^{-5} mm.) gave colourless prisms, m. p. 80—81·5° (Found: C, 50·2; H, 5·9. Calc. for $C_6H_8O_4$: C, 50·0; H, 5·6%). The m. p. was not depressed on admixture with authentic homoparaconic acid (m. p. 82—82·5°; Polyakova, Preobrazhenskii, and Preobrazhenskii, *J. Gen. Chem. Russia*, 1939, **9**, 1402).

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UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, December 19th*, 1946.]

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254. *Synthesis of ω-Aminoalkyl Cyanides.*

By ALAN A. GOLDBERG and WILLIAM KELLY.

A number of ω-aminoalkyl cyanides have been prepared by interaction of ω-bromoalkyl cyanides with potassium phthalimide followed by deacylation of the resulting ω-cyanoalkylphthalimides with hydrazine. The synthetic method would appear to be general for the production of any ω-aminoalkyl cyanide.

THE literature relating to aminoalkyl cyanides is not extensive. Aminomethyl cyanide (Klages, *J. pr. Chem.*, 1902, **65**, 188; Anslow and King, *J.*, 1929, 2463; Menge, *J. Amer. Chem. Soc.*, 1934, **56**, 2197), 1-aminoethyl cyanide (Dubsky, *Ber.*, 1916, **49**, 1048), 2-aminoethyl cyanide (Whitmore *et al.*, *J. Amer. Chem. Soc.*, 1944, **66**, 725), and 2-aminopropyl cyanide (Bruylants, *Bull. Soc. chim. Belg.*, 1923, **32**, 256) have been prepared by special methods not of general application. In addition, ω-aminoamyl cyanide has been prepared by the high pressure semihydrogenation of adiponitrile (U.S.PP. 2,208,598, 2,234,566).

ω-Aminoalkyl cyanides were required for the synthesis of a group of new aminoalkyl substituted heterocycles, and a convenient and general method was sought for their preparation. It has been found that ω-cyanoalkylphthalimides, readily available from potassium phthalimide and ω-bromoalkyl cyanides or from ω-bromoalkylphthalimides and potassium cyanide, can be deacylated with hydrazine by the Ing and Manske reaction (*J.*, 1926, 2348) with production of the aminoalkyl cyanide in substantial yield. It is of interest that the intermediate formed by the interaction of hydrazine and the phthalimidoalkyl cyanide yields phthalyl hydrazide and the aminoalkyl cyanide on acidification with hydrochloric acid without prolonged hydrolysis; this accords with the recent observations of Mosher (*J. Amer. Chem. Soc.*, 1946, **68**, 1565) on the decomposition of similar compounds. Deacylation with constant-boiling hydrochloric acid or by the modified method of Gabriel (cf. *Ber.*, 1911, **44**, 3632) with 5N-hydrochloric acid *via* the phthalamic acid is not possible owing to simultaneous hydrolysis of the cyano-group. Since various αω-alkylenediols are now available which are readily converted through the alkylene dibromides into the corresponding ω-bromoalkyl cyanides, and an αω-alkylene dibromide, $Br{\cdot}[CH_2]_n{\cdot}Br$, can be transformed into the ω-bromoalkyl cyanide, $Br{\cdot}[CH_2]_{n+1}{\cdot}CN$ (cf. Willstätter and Ettlinger, *Annalen*, 1903, **326**, 99; Leuchs, *Ber.*, 1911, **44**, 1510; Cheney and Piening, *J. Amer. Chem. Soc.*, 1945, **67**, 731; Breslow and Hansen, *ibid.*, p. 686), the method appears to be general for the synthesis of ω-aminoalkyl cyanides.

In this manner 3-amino-*n*-propyl cyanide, 5-amino-*n*-amyl cyanide, and 10-amino-*n*-decyl cyanide have been obtained. Contrary to the impression given by the literature the aminoalkyl cyanides are stable provided they are kept under anhydrous conditions. Protection of the amino-group by acylation allows the terminal cyano-group to undergo its functional reactions—*e.g.*, thioamide, imino-ether, and amidine transformation—and, often, subsequent formation of the 2-(acylamidoalkyl) heterocycle. The synthesis of a series of 2-(ω-aminoalkyl)-thiazoles and -pyrimidines from these acylamidoalkyl cyanides is described in the following paper; the synthesis of a number of 2-(ω-aminoalkyl)-iminazoles and -iminazolines will be reported shortly.

EXPERIMENTAL.

*3-Phthalimido-*n*-propyl Cyanide.*—A solution of potassium cyanide (75 g.) in water (150 c.c.) was added dropwise during 1½ hours to a stirred refluxing solution of trimethylene dibromide (202 g.) in alcohol (300 c.c.). Stirring at the reflux was continued for a further 1 hour, water (750 c.c.) added, and the solution extracted with chloroform (3 × 150 c.c.). The combined extracts after drying and

distillation yielded recovered trimethylene dibromide (41 g.), b. p. 55°/14 mm., 3-bromopropyl cyanide (45 g.), b. p. 90—92°/13 mm., and tetramethylene dicyanide (17 g.), b. p. 138—140°/13 mm. (cf. Gabriel, *Ber.*, 1889, **22**, 3336).

Potassium phthalimide (60 g.) was refluxed with a solution of 3-bromopropyl cyanide (44 g.) in absolute alcohol (200 c.c.) for 10 hours, alcohol (*ca.* 100 c.c.) distilled off, and the residual solution poured into water (1 l.). The oil which separated rapidly solidified (56 g.; m. p. 60°); it was collected and recrystallised from dilute methyl alcohol, *3-phthalimidopropyl cyanide* being obtained in white plates, m. p. 65—66° (Found: N, 13·2. $C_{12}H_{10}O_2N_2$ requires N, 13·1%).

3-Amino-n-propyl Cyanide.—Hydrazine hydrate (50% w/w solution; 25·5 g.) was added to a solution of the foregoing phthalimido-cyanide (40 g.) in alcohol (150 c.c.) at 50° and the resulting solution allowed to cool and kept at room temperature for 1 hour. Water (50 c.c.) was added, and the solution rendered just acid to Congo-red by concentrated hydrochloric acid, warmed to 60°, and kept for 2 hours. The insoluble phthalyl hydrazide was removed and the filtrate evaporated at reduced pressure at <40° to small volume. The residue was chilled, basified with 10N-sodium hydroxide (150 c.c.), extracted with ether (5 × 100 c.c.), the ethereal solution dried, and anhydrous alcoholic hydrogen chloride (10% w/w) added in order to precipitate the hydrochloride (10·5 g.; m. p. 134—136°); recrystallisation from anhydrous alcohol gave *3-amino-n-propyl cyanide hydrochloride* in white plates, m. p. 138—140° (Found: N, 23·0; Cl, 29·8. $C_4H_8N_2$,HCl requires N, 23·2; Cl, 29·5%). The hydrochloride (20 g.) was added to 10N-sodium hydroxide (50 c.c.) and the whole thoroughly extracted with ether; after drying over potassium carbonate the ethereal solution was distilled, *3-amino-n-propyl cyanide* being obtained as a colourless water soluble oil, b. p. 95—97°/20 mm. (Found: N, 33·8. $C_4H_8N_2$ requires N, 33·4%).

3-Benzamidopropyl Cyanide.—Benzoyl chloride (21 c.c.) was added dropwise during ½ hour to a rapidly stirred solution of sodium carbonate (25 g.) and 3-aminopropyl cyanide hydrochloride (20 g.) in water (200 c.c.) at 15°. Stirring at room temperature was continued for 2 hours, and the white insoluble *3-benzamidopropyl cyanide* collected, washed with water and dried in a vacuum; yield 25 g., m. p. 74—76°. For analysis a sample was recrystallised from aqueous methyl alcohol and obtained in colourless nacreous plates, m. p. 78—80° (Found: C, 70·0; H, 6·5; N, 15·1. $C_{11}H_{12}ON_2$ requires C, 70·3; H, 6·4; N, 14·9%).

5-Phthalimido-n-amyl Cyanide.—5-Bromopentanecarboxylic acid was obtained by the action of hydrobromic–sulphuric acids on the lactone mixture obtained by the potassium persulphate oxidation of *cyclo*hexanone (Brown and Partridge, *J. Amer. Chem. Soc.*, 1944, **66**, 839; Robinson and Smith, *J.*, 1937, 371). This was converted in 86% yield into the amide and the latter into 5-bromoamyl cyanide in 80% yield by the method of Breslow and Hansen (*J. Amer. Chem. Soc.*, 1945, **67**, 686).

Potassium phthalimide (50 g.) was refluxed with a solution of 5-bromoamyl cyanide (45 g.) in anhydrous alcohol (150 c.c.) for 24 hours. Alcohol (*ca.* 125 c.c.) was distilled off, water (125 c.c.) added, and the solution extracted with ether. Removal of the ether from the dried solution yielded 5-phthalimidoamyl cyanide (52 g.) as an oil which could not be induced to crystallise (cf. Albert, *Ber.*, 1909, **42**, 557).

5-Amino-n-amyl Cyanide.—Hydrazine hydrate (50% w/w aqueous solution; 72 g.) was refluxed with a solution of 5-phthalimidoamyl cyanide (152 g.) in alcohol (300 c.c.) for 1 hour and the solution left overnight. The solid mass was dissolved in water (1000 c.c.), the solution rendered just acid to Congo-red by the addition of 10N-hydrochloric acid (*ca.* 120 c.c.), and the precipitate of phthalyl hydrazide removed. The filtrate and washings were evaporated to small volume under reduced pressure at <40°, and the chilled residue was basified with 10N-sodium hydroxide and extracted with chloroform (3 × 100 c.c.). The extract was dried (K_2CO_3) and distilled, *5-aminoamyl cyanide* (52 g.) being obtained as a colourless oil, b. p. 116—118°/14 mm. (Found: N, 24·8. $C_6H_{12}N_2$ requires N, 25·0%).

A solution of the foregoing base (11·1 g.) and sodium carbonate (7·5 g.) in water (100 c.c.) was stirred at 15° and benzoyl chloride (11·3 c.c.) added slowly. Stirring was continued for a further 2 hours, and the precipitated 5-benzamidoamyl cyanide collected, washed with cold water, and dried in a vacuum; yield 18·6 g., m. p. 94—96°. A sample crystallised from benzene–ligroin in colourless acicular prisms, m. p. 98° (Found: C, 72·1; H, 7·4; N, 13·3. Calc. for $C_{13}H_{16}ON_2$: C, 72·2; H, 7·5; N, 13·0%). Von Braun and Steindorff (*Ber.*, 1904, **37**, 2915) prepared this compound from *N*-benzoylpiperidine and record m. p. 95° (cf. Ainley and King, *Proc. Roy. Soc.*, 1938, **125**, *B*, 60). A solution of 5-aminoamyl cyanide (2·0 g.) and sodium carbonate (3·5 g.) in 50% acetone (50 c.c.) was stirred at 20° with *p*-acetamidobenzenesulphonyl chloride (4·2 g.) for 1 hour. The *5-(p-acetamidobenzenesulphonamido)amyl cyanide* (5·1 g.; m. p. 112°) was filtered off and washed with water; it separated from dilute methyl alcohol in colourless plates, m. p. 114° (Found: N, 13·8; S, 10·5. $C_{14}H_{19}O_3N_3S$ requires N, 13·6; S, 10·4%).

10-Bromodecyl Cyanide.—A mixture of 10-bromodecanecarboxylic acid (102 g.; Ashton and Smith, *J.*, 1934, 438) and thionyl chloride (150 c.c.) was kept at room temperature for 1½ hours and then refluxed for a further ½ hour. The excess of thionyl chloride was distilled off at reduced pressure and the residual oil added slowly to rapidly stirred aqueous ammonia (*d* 0·88; 1000 c.c.) at 10°. Stirring was continued for a further 2 hours and the pale brown precipitate of 10-bromodecanecarboxylamide (98 g.; m. p. 84—86°) collected, washed with water, and dried in a vacuum. A sample crystallised from benzene in cream plates, m. p. 90° (Found: N, 5·6; Br, 29·8. Calc. for $C_{11}H_{22}ONBr$: N, 5·3; Br, 30·3%). In one preparation the crude acid chloride was distilled and obtained as a colourless oil, b. p. 176—178°/1 mm., but distillation was normally found to be unnecessary.

The foregoing amide (98 g.) was refluxed with thionyl chloride (100 c.c.) for 75 minutes. After removal of the excess thionyl chloride the residue was distilled and yielded *10-bromodecyl cyanide* (86 g.) as a pale golden oil, b. p. 158—164°/4 mm. (cf. Trunel, *Compt. rend.*, 1933, **197**, 453) (Found in redistilled sample: N, 5·5; Br, 31·9. $C_{11}H_{20}NBr$ requires N, 5·7; Br, 32·4%).

10-Phthalimidodecyl Cyanide.—10-Bromodecyl cyanide (84 g.) and potassium phthalimide (66 g.) were refluxed with alcohol (200 c.c.) for 24 hours. Alcohol (160 c.c.) was distilled off, and the residue, after the addition of water (500 c.c.), extracted with chloroform (2 × 150 c.c.). The extract was dried (K_2CO_3) and the chloroform removed to leave 10-phthalimidodecyl cyanide (97 g.) as a brown oil which failed to crystallise.

10-*Amino*-n-*decyl Cyanide*.—A solution of the foregoing phthalimidocyanide (76 g.) in methyl alcohol (200 c.c.) was refluxed for 1 hour with 50% w/w hydrazine hydrate (30 g.) and then kept at 20° overnight. Water (1000 c.c.) was added followed by 10N-hydrochloric acid until an acid reaction to Congo-red was obtained, the precipitate removed, and the filtrate evaporated to small volume at reduced pressure at <40°, the residue strongly basified with cold 10N-sodium hydroxide and extracted with chloroform. After drying over potassium carbonate, the chloroform solution yielded 10-*amino-decyl cyanide* as an amber water-soluble oil (29 g.), b. p. 138—142°/2 mm.; on redistillation it was obtained as a colourless oil, b. p. 136—138°/2 mm. (Found: N, 15·0. $C_{11}H_{22}N_2$ requires N, 15·4%).

Benzoyl chloride (7·8 g.) was added dropwise to a stirred mixture of the foregoing amino-cyanide (10·0 g.), sodium carbonate (10 g.), and water (100 c.c.) at 15°. Stirring was continued for 1 hour, and the precipitated 10-*benzamidodecyl cyanide* collected, washed with water and dried in a vacuum (15·4 g.; m. p. 54°); it crystallised from benzene–ligroin in colourless needles, m. p. 64° (Found: C, 75·4; H, 9·1; N, 10·0. $C_{18}H_{26}ON_2$ requires C, 75·5; H, 9·1; N, 9·8%).

Interaction of the aminocyanide with *p*-acetamidobenzenesulphonyl chloride in the presence of sodium carbonate in aqueous acetone in the same manner as described above yielded 10-(p-*acetamidobenzenesulphonamido*)*decyl cyanide*, which separated from aqueous methyl alcohol in colourless needles, m. p. 94° (Found: N, 11·3; S, 8·2. $C_{18}H_{29}O_3N_3S$ requires N, 11·1; S, 8·4%).

Aminomethyl Cyanide Hydrochloride.—Calcium carbonate (50 g.) was added portionwise to a rapidly stirred solution of aminomethyl cyanide sulphate (50 g.; *Org. Synth.*, Coll. Vol. I, 298) in water (200 c.c.). The excess of calcium carbonate and calcium sulphate were filtered off, and the solution acidified to Congo-red with hydrochloric acid and evaporated to dryness at reduced pressure at <40°. The residue was washed with a small amount of cold alcohol and recrystallised from methyl alcohol–diethyl ether, aminomethyl cyanide hydrochloride being obtained in colourless plates, m. p. 144—146°, which slowly turned purple in contact with the air (Found: N, 30·5; Cl, 37·9. Calc. for $C_2H_4N_2$,HCl: N, 30·3; Cl, 38·4%) (Menge, *loc. cit.*, gives m. p. 165° darkening at 135°).

Benzamidomethyl Cyanide.—Benzoyl chloride (50 g.) was added dropwise to a rapidly stirred solution of aminomethyl cyanide sulphate (50 g.) and sodium carbonate (70 g.) in water (150 c.c.), the temperature not being allowed to exceed 15°. Stirring was continued at room temperature for 8 hours, and the white insoluble *benzamidomethyl cyanide* collected, washed with water, and dried; yield 44 g., m. p. 136—138°. A sample crystallised from methyl alcohol in colourless rectangular plates, m. p. 142—144° (Found: N, 17·7. $C_9H_8ON_2$ requires N, 17·5%).

p-*Acetamidobenzenesulphonamidomethyl Cyanide* (cf. Cocker, *J.*, 1940, 1574).—Sodium carbonate (20 g.) was added to a cold rapidly stirred solution of aminomethyl cyanide sulphate (16·4 g.) in water (50 c.c.); acetone (80 c.c.) was added followed by finely divided *p*-acetamidobenzenesulphonyl chloride (20 g.), and the mixture stirred at room temperature for 3 hours. After the addition of water (50 c.c.) the insoluble *p*-acetamidobenzenesulphonamidomethyl cyanide (17 g.; m. p. 190—192°) was collected, washed with water, and dried; a sample separated from ethyl alcohol in colourless leaves, m. p. 192° (Found: N, 16·8; S, 12·8. Calc. for $C_{10}H_{11}O_3N_3S$: N, 16·6; S, 12·7%).

1-*Aminoethyl Cyanide* (cf. Dubsky, *loc. cit.*).—A solution of potassium cyanide (80 g.) in water (200 c.c.) was added slowly to a stirred mixture of ammonium chloride (72 g.), ether (600 c.c.), and acetaldehyde (32 g.) at 10°. Stirring was continued for 12 hours at 15°, the ether layer separated, and the aqueous layer extracted with ether (2 × 100 c.c.). The combined ether solutions were *completely* dried over ignited potassium carbonate, the ether removed, and the residual oil distilled, 1-aminoethyl cyanide (25 g.) being obtained as a colourless oil, b. p. 53—55°/14 mm. A sample which had been kept for 6 months at 20° under anhydrous conditions redistilled at the same b. p. leaving no residue; a sample kept in the presence of moisture became full of crystalline solid after several weeks. The hydrochloride was obtained in colourless needles, m. p. 144—146°, by the addition of absolute ethereal hydrogen chloride to a solution of the base in absolute alcohol (Found: N, 26·7; Cl, 33·3. $C_3H_6N_2$,HCl requires N, 26·3; Cl, 33·3%).

1-*Benzamidoethyl Cyanide*.—Benzoyl chloride (19 g.) was added dropwise to a stirred solution of 1-aminoethyl cyanide (8·6 g.) and sodium carbonate (10 g.) in water (20 c.c.) maintained at 15° by external cooling. Stirring was continued for 10 hours, and the precipitate of 1-*benzamidoethyl cyanide* (15·0 g.; m. p. 102—104°) collected, washed with cold water and dried in a vacuum; a sample separated from benzene in colourless needles, m. p. 108° (Found: C, 68·9; H, 5·8; N, 16·4. $C_{10}H_{10}ON_2$ requires C, 69·0; H, 5·8; N, 16·1%).

2-*Benzamidoethyl Cyanide*.—2-Aminoethyl cyanide was obtained by the method of Whitmore *et al.* (*loc. cit.*). The best yields were obtained by standing the mixture of vinyl cyanide and ammonia at *ca.* 30° for 48 hours in a glass pressure bottle; 120 g. of freshly distilled vinyl cyanide yielded 40 g. of 2-aminoethyl cyanide, b. p. 80—85°/17 mm., and 80 g. of bis-compound, b. p. 200—220°/12 mm. It was found essential to use a 10-inch Vigreux column for removal of the aqueous ammonia since the aminocyanide is slightly volatile in water vapour.

Benzoyl chloride (80 c.c.) and 5N-sodium hydroxide (180 c.c.) were added simultaneously to a rapidly stirred solution of the foregoing amino-cyanide (40 g.) in water (120 c.c.) in such a manner that the mixture was maintained throughout at 10—12° and at pH 8·5—10·0. After the addition (45 minutes) the mixture was stirred at room temperature for a further 2 hours, and the 2-benzamidoethyl cyanide filtered off, washed with dilute sodium carbonate and water, and dried in a vacuum at 20—30°. Yield, 92 g. of a white powder, m. p. 94—96°, which was pure enough for further use; a sample crystallised from 10% alcohol in colourless needles, m. p. 96—98° (Found: N, 16·3. Calc. for $C_{10}H_{10}ON_2$: N, 16·1%).

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255. *Synthesis of the 2-ω-Aminoalkyl and 2-ω-Sulphanilamidoalkyl Derivatives of Thiazole and Pyrimidine.*

By Alan A. Goldberg and William Kelly.

4 : 6-Dimethyl-2-aminomethylpyrimidine and a series of 4-methyl-2-ω-aminoalkylthiazoles have been synthesised from the acylamidoalkyl cyanides described in the previous communication. From these new bases homologues of 2-sulphanilamido-4-methylthiazole and 2-sulphanilamido-4 : 6-dimethylpyrimidine have been prepared for examination as bacterial inhibitors.

Homologues of sulphanilamide containing the homologising methylene chain between the amino-group and the benzene ring and between the latter and the sulphonamide residue have previously been reported (Miller, Sprague, Kissinger, and McBurney, *J. Amer. Chem. Soc.*, 1940, **62**, 2099; G.P. 726382; Klarer, *Die Chemie*, 1943, **56**, 10; Bergeim and Braker, *J. Amer. Chem. Soc.*, 1944, **66**, 1459). In addition, similar homologues of 2-sulphanilamidothiazole (sulphathiazole) and 2-sulphanilamido-4 : 6-dimethylpyrimidine (sulphadimethylpyrimidine) have been prepared (Bergeim and Braker, *loc. cit.*) and shown to possess activities of a rather lower order against experimental *Cl. perfringens* infections than α-aminotoluene-*p*-sulphonamide (marfanil) (Hamre *et alii*, *Proc. Soc. Exp. Biol. Med.*, 1944, **55**, 170; compare also Maclennan, *Lancet*, 1943, **265**, 123; Schreus and Peltzer, *Klin. Wochenschr.*, 1941, **20**, 1233, 1250; Schreus, *ibid.*, 1942, **21**, 14; Domagk, *ibid.*, p. 448; Klöse and Schrober, *Zentr. Bakt.*, 1942, **149**, 15). It was accordingly of interest to synthesise a series of homologues of sulphathiazole and sulphadimethylpyrimidine in which the homologising chain occupies a position between the sulphonamido-residue and the heterocycle for examination as bacterial inhibitors.

Two methods were employed which would appear to be of general application for the preparation of this type of homosulphathiazole. Conversion of the ω-benzamidoalkyl or ω-phthalimidoalkyl cyanide into the corresponding thioamide, formation of the thiazole ring by condensation with an α-halogeno-aldehyde or -ketone, and hydrolysis of the product readily yielded the 2-(ω-aminoalkyl)thiazole; this was converted by the normal route into the 2-(ω-sulphanilamidoalkyl)thiazole. Alternatively, the ω-acetylsulphanilamidoalkyl cyanide was transformed into the thioamide, the latter treated with the α-halogeno-aldehyde or -ketone, and the resulting 2-(ω-acetylsulphanilamidoalkyl)thiazole deacetylated with aqueous alkali. The overall yields of the 2-aminoalkylthiazoles and 2-(ω-sulphanilamidoalkyl)thiazoles were of a high order with the lower members and also with the highest member of the series. With 5-acylamidoamyl cyanide, however, the normal procedure of hydrogen sulphide addition in the presence of ammonium sulphide gave the corresponding thioamide in yields of the order of only 25%; use of ethanolamine (Yuoh-Fong Chi, *J. Amer. Chem. Soc.*, 1942, **64**, 90) and alkali ethoxide as catalysts (Erlenmeyer, *Helv. Chim. Acta*, 1944, **27**, 412) failed to effect improvement. The α-halogeno-ketones employed were chloroacetone, ethyl α-chloroacetoacetate, ethyl γ-bromoacetoacetate, and ethyl bromopyruvate. It is of interest that a sample of ethyl α-chloroacetoacetate obtained by the action of sulphuryl chloride on ethyl acetoacetate after standing in diffused daylight in a closed bottle for 12 months gave the same high yield of ethyl 4-methyl-2-benzamidomethylthiazole-5-carboxylate on condensation with benzamidothioacetamide as did the freshly prepared compound, whereas Epprecht (*Annalen*, 1894, **278**, 79) states that ethyl α-bromoacetoacetate is not stable and on standing for several weeks isomerises in part to the γ-bromo-compound.

The 4-methyl-2-aminoalkylthiazoles are stable, distillable oils, very soluble in dilute acid; the 4-methyl-2-sulphanilamidoalkylthiazoles are well-crystallised compounds with much lower melting points than sulphathiazole and with considerably more solubility than the latter in water and dilute organic acids. The displacement of the thiazole ring from its adjacence to the sulphonamido-residue allows the basic function of the heterocycle, masked in 2-acetylsulphanilamidothiazole, to reappear; for example, the 2-acetylsulphanilamidoalkylthiazoles are easily soluble in cold aqueous mineral acid, whereas 2-acetylsulphanilamidothiazole is completely insoluble.

Less success was obtained in the case of the attempted preparation of a range of homosulphamethazines. Both benzamidomethyl cyanide and acetylsulphanilamidomethyl cyanide readily yielded the corresponding imino-ethers and amidines and these condensed with acetylacetone to give 4 : 6-*dimethyl*-2-*benzamidomethyl*- and -2-*acetylsulphanilamidomethylpyrimidine*; hydrolysis of the former with acid and the latter with dilute alkali gave respectively 4 : 6-*dimethyl*-2-*aminomethylpyrimidine* and 4 : 6-*dimethyl*-2-*sulphanilamidomethylpyrimidine*. Benzamidoacetamidine reacted readily with ethyl cyanoacetate but failed to give the expected

pyrimidine derivative; elimination of ammonia from the amidine residue and the reactive methylene group of the ester occurred with formation of *ethyl* (1-*amino*-2-*benzamidoethylidene*)-*cyanoacetate* in good yield. With malononitrile, benzamidoacetamidine reacted in the same manner with production of 1-*amino*-2-*benzamidoethylidenemalononitrile*; compare the similar condensation of ethyl cyanoacetate with formamidine and with benzamidine in the absence of alkali (Kenner *et alii*, *J.*, 1943, 388). The higher homologues of benzamidoacetamidine could not be induced to condense with acetylacetone under any of the varied reaction conditions employed.

Antibacterial Activities.—Infections of medium and low density with *Streptococcus hæmolyticus* (Aronson) were induced in mice by intraperitoneal inoculation of 0·5 c.c. of a 1 : 2000 dilution of a 24-hours old broth subculture of organisms of different virulence; the M.L.D. of the standard organism was 0·5 c.c. of a 1 : 32,000 dilution of the 24-hour old subculture, while the other organism used had been attenuated until the M.L.D. of the 24-hour old subculture was 0·5 c.c. of a 1 : 8000 dilution. Oral administration of daily divided doses of 200—300 mg./kg. of the 4-methyl-2-sulphanilamidoalkylthiazoles, Nos. 1423, 1424, 1432, 1433, 1323, and of the sulphanilamidomethyl-4 : 6-dimethylpyrimidine, No. 1427, failed to give complete protection to the mice; in the controls daily administration of 100 mg./kg. of sulphathiazole or sulphadiazine or 150 mg./kg. of sulphanilamide effected complete protection. All the compounds showed a small but nevertheless definite activity in daily doses of 400 mg./kg.

The activity of these homosulphonamides against *Cl. perfringens* infections in mice will be reported elsewhere.

Experimental.

(The acylamidoalkyl cyanides used are described in the previous paper.)

Benzamidothioacetamide.—Ammonia was passed into methyl alcohol (200 c.c.) until the increase in weight was 20 g., followed by hydrogen sulphide until 40 g. had been absorbed. Benzamidomethyl cyanide (50 g.) was added, and the resulting solution kept in a closed vessel at room temperature for 36—48 hours with occasional shaking. After the addition of water (500 c.c.) and standing for 12 hours, *benzamidothioacetamide* (40 g.; m. p. 152—154°) separated in small crystals. For analysis a sample was recrystallised from aqueous methyl alcohol and obtained in stout colourless prisms, m. p. 154° (Found: N, 14·7; S, 16·6. $C_9H_{10}ON_2S$ requires N, 14·4; S, 16·5%).

4-*Methyl*-2-*benzamidomethylthiazole.*—A solution of the foregoing thioamide (31 g.) in methyl alcohol (300 c.c.) and pyridine (25 c.c.) was refluxed with chloroacetone (23 c.c.) for 2 hours. The methyl alcohol was distilled off, water (200 c.c.) added, and the precipitated 4-*methyl*-2-*benzamidomethylthiazole* collected (35 g.; m. p. 108°). A sample separated from aqueous methyl alcohol in pale cream needles, m. p. 114—116° (Found: N, 12·3; S, 13·5. $C_{12}H_{12}ON_2S$ requires N, 12·1; S, 13·8%).

4-*Methyl*-2-*aminomethylthiazole.*—A solution of 4-methyl-2-benzamidomethylthiazole (35 g.) in 5N-hydrochloric acid (225 c.c.) was refluxed for 3 hours, cooled, the precipitate of benzoic acid removed, and the filtrate evaporated to small volume at reduced pressure. The residue was strongly basified with 10N-sodium hydroxide and extracted with ether (3 × 100 c.c.); after drying over potassium carbonate and distillation, the ethereal extract yielded 4-*methyl*-2-*aminomethylthiazole* (13·5 g.) as a colourless oil, b. p. 82—84°/5 mm. (Found: N, 22·1; S, 24·7. $C_5H_8N_2S$ requires N, 21·8; S, 25·0%).

4-*Methyl*-2-*sulphanilamidomethylthiazole* (No. 1423).—4-Methyl-2-aminomethylthiazole (2·5 g.) was heated on the water-bath for ½ hour with a solution of acetylsulphanilyl chloride (4·7 g.) in anhydrous pyridine (10 c.c.). The mixture was cooled, diluted with water, and the precipitated 4-*methyl*-2-*acetylsulphanilamidomethylthiazole* (4·9 g.) collected; this crystallised from aqueous alcohol in cream leaves, m. p. 176° (Found: N, 13·1; S, 19·3. $C_{13}H_{15}O_3N_3S_2$ requires N, 12·9; S, 19·7%).

The foregoing acetamido-compound (4·0 g.) was heated with 2·5N-sodium hydroxide (32 c.c.) at 100° for 1 hour, the solution diluted with water, partly neutralised with acetic acid, the filtered solution (charcoal) acidified with acetic acid, and the precipitate collected. Recrystallisation from aqueous alcohol yielded 4-*methyl*-2-*sulphanilamidomethylthiazole* (3·1 g.) in colourless plates, m. p. 124—126° (Found: N, 14·6; S, 23·0. $C_{11}H_{13}O_2N_3S_2$ requires N, 14·8; S, 22·6%).

4-*Methyl*-2-*aminomethylthiazole*-5-*carboxylic Acid.*—A solution of β-benzamidothioacetamide (19·4 g.) in anhydrous methyl alcohol (225 c.c.) and anhydrous pyridine (12 c.c.) was refluxed with ethyl α-chloroacetoacetate (18 c.c.; Dey, *J.*, 1915, **107**, 1646) for 5 hours. The solvent was distilled off to incipient crystallisation, and the solution (70 c.c.) chilled, *ethyl* 4-*methyl*-2-*benzamidomethylthiazole*-5-*carboxylate* (25 g.; m. p. 140°) separating in long colourless needles; by evaporation of the filtrate a further crop (1·5 g.) was obtained (Found, in recrystallised material, m. p. 140—142°: N, 8·9; S, 10·4. $C_{15}H_{16}O_3N_2S$ requires N, 9·2; S, 10·5%).

A solution of the foregoing benzamido-compound (6·1 g.) in methyl alcohol (50 c.c.) was refluxed with 5N-sodium hydroxide (10 c.c.) for 1 hour. After standing overnight at 20° the alcohol was distilled away at reduced pressure, the residue dissolved in water (70 c.c.), filtered (charcoal), and the solution adjusted to pH 4 with hydrochloric acid; 4-*methyl*-2-*benzamidomethylthiazole*-5-*carboxylic acid* (5·0 g.) separated as a microcrystalline precipitate. The acid crystallised from 50% alcohol in glittering white tablets, m. p. 252—254° (decomp.) (Found: N, 10·3; S, 11·7. $C_{13}H_{12}O_3N_2S$ requires N, 10·2; S, 11·6%).

A solution of crude ethyl 4-methyl-2-benzamidomethylthiazole-5-carboxylate (15 g.) in methyl alcohol (200 c.c.) was refluxed with 10N-hydrochloric acid (100 c.c.) for 14 hours. The solution was distilled in a current of steam to remove alcohol and benzoic acid and, after the addition of more hydrochloric acid, evaporated to very small volume; on cooling, 4-*methyl*-2-*aminomethylthiazole*-5-*carboxylic acid hydrochloride* separated in small prisms (6 g.), m. p. 248—250° (decomp.) (Found, in material dried at 120°/1 mm. over phosphoric oxide: N, 13·7; Cl, 16·8. $C_6H_8O_2N_2S,HCl$ requires N, 13·5; Cl, 16·9%).

The foregoing hydrochloride (5 g.) was dissolved in water (12 c.c.) and the solution adjusted to pH 3·5—4·0 by addition of 5N-sodium hydroxide (*ca.* 6 c.c.). When the resulting solution was kept on ice, *4-methyl-2-aminomethylthiazole-5-carboxylic acid* (2·8 g.) separated in white plates; these crystallised from 50% alcohol in stellate clusters of colourless feathers, m. p. 282—284° (Found: N, 16·4; S, 18·5. $C_6H_8O_2N_2S$ requires N, 16·3; S, 18·6%).

2-Benzamidomethyl-4-thiazolylacetic Acid.—A solution of benzamidomethylthioacetamide (9·7 g.) in anhydrous methyl alcohol (150 c.c.) and anhydrous pyridine (6 c.c.) was refluxed with ethyl γ-bromoacetoacetate (8·5 c.c.; Epprecht, *loc. cit.*) for 4½ hours. The solvent was distilled away at reduced pressure, the residual oil dissolved in warm 1·5N-hydrochloric acid (200 c.c.), and the solution filtered (charcoal) and adjusted to pH 7 with dilute sodium hydroxide; *ethyl 2-benzamidomethyl-4-thiazolylacetate* (12·5 g.) separated, which crystallised from benzene–ligroin in glittering plates, m. p. 86—88° (Found: N, 9·6; S, 10·9. $C_{15}H_{16}O_3N_2S$ requires N, 9·7; S, 11·0%).

A solution of the foregoing crude benzamido-compound (6 g.) in methyl alcohol (60 c.c.) and 5N-sodium hydroxide (10 c.c.) was refluxed for 1 hour. The solvent was removed at reduced pressure, the residue dissolved in a small volume of water, and the filtered solution adjusted to pH 4 with hydrochloric acid; *2-benzamidomethyl-4-thiazolylacetic acid* (3 g.) separated in colourless plates, which crystallised from dilute alcohol in glittering plates, m. p. 184—186° (Found: N, 10·3; S, 11·6. $C_{13}H_{12}O_3N_2S$ requires N, 10·2; S, 11·6%).

2-Benzamidomethylthiazole-4-carboxylic Acid.—A solution of freshly prepared and redistilled pyruvic acid (75 g.; 60 c.c.) and toluenesulphonic acid (6 g.) in ethyl alcohol (1250 c.c.) and benzene (300 c.c.) was refluxed under a 12" Widmer column with a 10 : 1 reflux ratio and solvent removed at the rate of 100 c.c./hour. After 5 hours a further quantity of benzene (300 c.c.) was added and the distillation continued for another 4 hours, solvent being removed at the rate of 240—250 c.c./hour. After standing overnight the residual oil was distilled through a 6" Vigreux column, the solvent being removed first at 760 mm. up to 80° to avoid loss of ester; redistillation of the fraction, b. p. 50—65°/20 mm. (75 g.), yielded 68 g. of ethyl pyruvate as a colourless oil, b. p. 54—60°/20 mm. A solution of dry bromine (25 c.c.) in dry carbon tetrachloride (25 c.c.) was added dropwise during ½ hr. to a refluxing solution of ethyl pyruvate (58 g.) in carbon tetrachloride (100 c.c.). After standing for 3 hours, the oil was distilled and yielded a fraction (82 g.), b. p. 96—100°/10 mm., which on redistillation gave ethyl bromopyruvate (70 g.), b. p. 90—94°/8 mm.

A solution of benzamidothioacetamide (9·7 g.) in dioxan (110 c.c.) and benzene (40 c.c.) was heated on the water-bath with ethyl bromopyruvate (8 c.c.) for 2 hours. The solvent was *rapidly* distilled away at reduced pressure, the residual oil dissolved in 1·7N-hydrochloric acid (300 c.c.), and the solution filtered (charcoal), adjusted at 20° with stirring to pH 7·6 by addition of 5N-sodium hydroxide, and the precipitate of *ethyl 2-benzamidomethylthiazole-4-carboxylate* (5·0 g.; m. p. 76—80°) collected. Adjustment of the filtrate to pH 2·8—3·0 with hydrochloric acid effected precipitation of *2-benzamidomethylthiazole-4-carboxylic acid* (5·8 g.; m. p. 176—180°). The ester crystallised from benzene–ligroin in colourless plates, m. p. 82—84° (Found: N, 9·7; S, 10·9. $C_{14}H_{14}O_3N_2S$ requires N, 9·7; S, 11·0%); the acid separated from dilute alcohol in glittering colourless leaves, m. p. 180—182° (Found: N, 10·4; S, 11·9. $C_{12}H_{10}O_3N_2S$ requires N, 10·7; S, 12·2%). Interaction of the thioamide and ethyl bromopyruvate in alcoholic solution in the presence of pyridine yielded a dark gum.

Benzamidoacetamidine Hydrochloride.—A mixture of benzamidomethyl cyanide (40 g.), anhydrous chloroform (300 c.c.), and anhydrous ethyl alcohol (59 c.c.) was saturated at 5° with dry hydrogen chloride; the cyanide dissolved as the hydrogen chloride was passed in and then set to a crystalline mass which redissolved as the solution became saturated. After standing at 4° for 16—20 hours, the chloroform was pumped off at room temperature, and the crystalline residue (53 g.; m. p. 144—146°) of *benzamidoacetiminoether hydrochloride*, containing ammonium chloride as impurity, was washed with a little dry chloroform and dried in a vacuum (Found: N, 12·2; Cl, 15·8. $C_{11}H_{14}O_2N_2,HCl$ requires N, 11·5; Cl, 14·6%). This was added to alcohol (300 c.c.; lime-dried), which had been previously saturated with dry ammonia at 5°, and the mixture swirled at room temperature until solution was obtained and then allowed to stand in a closed vessel at *ca.* 4° for 24 hours. After addition of absolute ether (200 c.c.), the crystalline precipitate of *benzamidoacetamidine hydrochloride* (44 g.), m. p. 184—186°, was collected and dried in a vacuum over sulphuric acid; from alcohol–ether a sample separated in colourless nacreous plates, m. p. 187° (Found: N, 20·1; Cl, 17·1. $C_9H_{11}ON_3,HCl$ requires N, 19·7; Cl, 16·6%). The free amidine, m. p. 132—134°, precipitated by the addition of 5N-sodium hydroxide to a cold 20% aqueous solution of the hydrochloride, was unstable and rapidly became converted into benzamidoacetamide, which crystallised from boiling water in large colourless prisms, m. p. 186° (Found: C, 60·8; H, 5·8; N, 16·1. Calc. for $C_9H_{10}O_2N_2$: C, 60·6; H, 5·7; N, 15·7%).

4 : 6-Dimethyl-2-benzamidomethylpyrimidine.—A solution of benzamidoacetamidine hydrochloride (30 g.) in alcohol (150 c.c.) was refluxed with anhydrous potassium carbonate (20 g.) and acetylacetone (18 g.) for 4 hours. The alcohol was distilled off, water added to the residue, and the precipitated oil, which slowly solidified to a dark gum, lixiviated with warm dilute hydrochloric acid and, after chilling, the insoluble benzamidoacetamide removed. Basification of the filtrate with 5N-sodium hydroxide precipitated *4 : 6-dimethyl-2-benzamidomethylpyrimidine* (8·7 g.; m. p. 192—194°), which crystallised from aqueous methyl alcohol (charcoal) in slender colourless needles, m. p. 200° (Found: C, 69·6; H, 6·3; N, 17·8. $C_{14}H_{15}ON_3$ requires C, 69·7; H, 6·3; N, 17·4%). Many modifications of the above procedure failed to increase the yield.

4 : 6-Dimethyl-2-aminomethylpyrimidine.—A solution of crude 4 : 6-dimethyl-2-benzamidopyrimidine (36·5 g.) in 5N-hydrochloric acid (225 c.c.) was refluxed for 4 hours, cooled, the precipitate of benzoic acid removed, and the filtrate evaporated to dryness under reduced pressure. The residual hydrochloride was dissolved in warm water (200 c.c.), filtered (charcoal), evaporated under reduced pressure to small volume (100 c.c.), chilled, and strongly basified with 5N-sodium hydroxide. After standing, the precipitate was collected (22 g.; m. p. 152—156°), drained, boiled with water (250 c.c.), the unchanged benzamido-compound (4·0 g.) removed, and the filtered solution allowed to cool; *4 : 6-dimethyl-2-aminomethylpyrimidine* (17 g.) separated in colourless, hydrated, felted needles which on drying at 100° yielded an

anhydrous white powder, m. p. 168° (Found: C, 61·4; H, 8·1; N, 30·9. $C_7H_{11}N_3$ requires C, 61·3; H, 8·1; N, 30·6%). The *monohydrochloride* separated from methyl alcohol–ether in slender white needles, m. p. 244—246° (Found: N, 24·3. $C_7H_{11}N_3$,HCl requires N, 24·2%).

Acetylsulphanilamidoacetamidine Hydrochloride.—A mixture of acetylsulphanilamidomethyl cyanide (14·6 g.), dry chloroform (100 c.c.), and absolute ethyl alcohol (13·7 c.c.) was saturated with dry hydrogen chloride at 5° and then kept at *ca.* 4° for 7 days with occasional shaking. The solvents were pumped off at room temperature, the residue mixed with anhydrous alcohol (100 c.c.) which had previously been saturated with dry ammonia, and the solution, which rapidly crystallised, allowed to stand at room temperature for 16 hours. The solvent was pumped off, and the crystalline residue (16 g.; m. p. 160°) of *acetylsulphanilamidoacetamidine hydrochloride* washed with ether. For analysis a sample was recrystallised from alcohol–ether and obtained in white needles, m. p. 164—166° (Found: N, 19·0; Cl, 12·0. $C_{10}H_{14}O_3N_4S$,HCl requires N, 18·5; Cl, 11·8%). The free amidine was precipitated from the concentrated aqueous solution of the hydrochloride by 5N-sodium hydroxide but rapidly decomposed to *acetylsulphanilamidoacetamide*, which crystallised from boiling water in colourless rectangular prisms, m. p. 218—220° (Found: C, 44·1; H, 5·0; N, 16·0. $C_{10}H_{13}O_4N_3S$ requires C, 44·2; H, 4·8; N, 15·9%).

4 : 6-*Dimethyl-2-sulphanilamidomethylpyrimidine* (No. 1427).—Acetylsulphanilamidoacetamidine hydrochloride (10 g.), acetylacetone (6·0 c.c.), pyridine (14 c.c.), and water (6 c.c.) were heated together at 100° for 4 hours. Water (20 c.c.) was added, and the precipitate (4·8 g.; m. p. 256°) collected and recrystallised from aqueous alcohol, 4 : 6-*dimethyl-2-acetylsulphanilamidomethylpyrimidine* being obtained in slender cream needles, m. p. 260—262° (Found: C, 53·7; H, 5·3; N, 17·2. $C_{15}H_{18}O_3N_4S$ requires C, 53·9; H, 5·4; N, 16·9%).

The foregoing acetamido-compound (7·8 g.) was dissolved in 2·5N-sodium hydroxide (62 c.c.), and the solution heated on the water-bath for 1 hour, cooled, partly neutralised with dilute hydrochloric acid, and filtered (charcoal). Adjustment of the filtrate to pH 7·0 effected separation of 4 : 6-*dimethyl-2-sulphanilamidomethylpyrimidine* (6·6 g.) in microscopic needles, m. p. 230—232°, which after a further crystallisation from aqueous alcohol had m. p. 232—234° (Found: N, 19·4; S, 11·0. $C_{13}H_{16}O_2N_4S$ requires N, 19·2; S, 10·6%).

The compound was also obtained by the following route. Acetylsulphanilyl chloride (3 g.) was added to a solution of 4 : 6-dimethyl-2-aminomethylpyrimidine (2 g.) and sodium hydrogen carbonate (2 g.) in 60% acetone (50 c.c.). After being warmed on the water-bath for a short time, the mixture was diluted with water, and the precipitate collected. Crystallisation from aqueous alcohol yielded 4 : 6-dimethyl-2-acetylsulphanilamidomethylpyrimidine in cream needles, m. p. 261—262°, alone and in admixture with a sample prepared as above described.

Condensation of Benzamidoacetamidine with Malononitrile: 1-Amino-2-benzamidoethylidenemalononitrile.—A solution of benzamidoacetamidine hydrochloride (21·3 g.) in anhydrous alcohol (150 c.c.) was converted into the free amidine base by addition of a solution of sodium (2·3 g.) in alcohol (50 c.c.). Malononitrile (7·5 c.c.) was added, and the solution allowed to stand at 40—45°; the mixture rapidly turned orange and in 2 hours developed an ammoniacal odour and began depositing crystals. After 48 hours at this temperature the mixture was chilled, and the crystalline, almost colourless precipitate of 1-*amino-2-benzamidoethylidenemalononitrile* (25·5 g.; m. p. 206°) collected. A sample crystallised from dilute alcohol in colourless, glistening leaves, m. p. 220—222° (decomp.) with softening at 210° (Found, in material dried at 80°/2 mm. over phosphoric oxide: C, 63·6; H, 4·5; N, 24·9, 25·0. $C_{12}H_{10}ON_4$ requires C, 63·8; H, 4·4; N, 24·8%).

Condensation of Benzamidoacetamidine with Ethyl Cyanoacetate: Ethyl 1-Amino-2-benzamidoethylidenecyanoacetate.—A mixture of ethyl cyanoacetate (12·4 g.) and an anhydrous alcoholic solution of benzamidoacetamidine (prepared as in the foregoing example from 21·3 g. of benzamidoacetamidine hydrochloride in 150 c.c. alcohol and 2·3 g. of sodium in 50 c.c. alcohol) was kept for 48 hours at 40°; crystals rapidly separated with development of an ammoniacal odour. The mixture was chilled, and the crystalline precipitate of *ethyl 1-amino-2-benzamidoethylidenecyanoacetate* (24 g.; m. p. 196°) collected. A sample separated from dilute alcohol in colourless felted leaves, m. p. 198—200° (Found: C, 61·3; H, 5·4; N, 15·6, 15·5. $C_{14}H_{15}O_3N_3$ requires C, 61·5; H, 5·5; N, 15·4%).

α-Benzamidothiopropionamide.—α-Benzamidopropionitrile (11·2 g.) was added to freshly prepared methanolic ammonium sulphide (obtained by dissolution of 6 g. of ammonia and then 6 g. of hydrogen sulphide in 75 c.c. of methyl alcohol) and the solution kept in a sealed bottle at room temperature for 16 hours. On dilution with water *α-benzamidothiopropionamide* (7·6 g.) slowly separated; this crystallised from aqueous methyl alcohol in colourless needles, m. p. 146° (Found: N, 13·8; S, 15·4. $C_{10}H_{12}ON_2S$ requires N, 13·5; S, 15·4%).

4-Methyl-2-(1′-aminoethyl)thiazole.—A solution of the foregoing amide (50 g.) in methyl alcohol (200 c.c.) and pyridine (38 c.c.) was refluxed with chloroacetone (24 c.c.) for 2 hours, and the alcohol then distilled off. Addition of water to the residue precipitated *4-methyl-2-(1′-benzamidoethyl)thiazole* (50 g.), which crystallised from aqueous methyl alcohol in colourless needles, m. p. 112° (Found: N, 11·6; S, 13·4. $C_{13}H_{14}ON_2S$ requires N, 11·4; S, 13·0%).

A solution of the foregoing crude compound (50 g.) in 5N-hydrochloric acid (400 c.c.) was refluxed for 7 hours, cooled, the benzoic acid removed, and the filtrate evaporated almost to dryness at reduced pressure. Water (300 c.c.) was added, and the solution evaporated to very small volume, cooled, strongly basified with 10N-sodium hydroxide, and extracted with chloroform (2 × 50 c.c.). After drying and distillation, the chloroform extracts yielded *4-methyl-2-(1′-aminoethyl)thiazole* as a colourless oil (21 g.), b. p. 98—100°/12 mm. (Found: N, 20·0; S, 22·5. $C_6H_{10}N_2S$ requires N, 19·7; S, 22·6%).

α-Acetylsulphanilamidothiopropionamide.—α-Acetylsulphanilamidopropionitrile (9·2 g.) was added to freshly prepared methanolic ammonium sulphide (5 g. of ammonia and 5 g. of hydrogen sulphide in 100 c.c. of methyl alcohol), and the mixture kept at 20° with frequent shaking for 24 hours. Addition of water (150 c.c.) caused the *thio-amide* (6·6 g.) slowly to separate in colourless prisms, m. p. 220; these crystallised from aqueous methyl alcohol in stout prisms, m. p. 226° (Found: N, 14·2; S, 21·1. $C_{11}H_{13}O_3N_3S_2$ requires N, 14·0; S, 21·3%).

4-Methyl-2-(1′-sulphanilamidoethyl)thiazole (No. 1424).—A solution of the foregoing amide (5·0 g.) in

alcohol (50 c.c.), water (5 c.c.), and pyridine (4 c.c.) was refluxed with chloroacetone (2·4 g.) for 2 hours, and the alcohol then distilled off. Addition of water (50 c.c.) precipitated *4-methyl-2-(1′-acetylsulphanilamidoethyl)thiazole* (5·2 g.; m. p. 172°) which crystallised from aqueous alcohol in pale cream needles, m. p. 180—182° (Found: N, 12·3; S, 18·6. $C_{14}H_{17}O_3N_3S_2$ requires N, 12·4; S, 18·9%).

Hydrolysis of the foregoing compound (4·2 g.) with 2·5N-sodium hydroxide at 100° for 1 hour yielded *4-methyl-2-(1′-sulphanilamidoethyl)thiazole* (2·4 g.), which separated from dilute alcohol in colourless prisms, m. p. 168° (Found: N, 14·5; S, 21·3. $C_{12}H_{15}O_2N_3S_2$ requires N, 14·2; S, 21·6%).

β-Benzamidothiopropionamide.—A solution of β-benzamidopropionitrile (42 g.) in 96% alcohol (325 c.c.) containing 3·3% w/w ammonia was saturated with hydrogen sulphide and kept at *ca.* 40° for 5 days, more hydrogen sulphide being added each day. Solvent was pumped off from the semi-solid mixture, ether in excess added, and the precipitate collected. This was dissolved in 90% methyl alcohol (500 c.c.), the sulphur removed, and the filtrate evaporated to incipient crystallisation (vol. 250 c.c.); on standing in the ice chest, *β-benzamidothiopropionamide* (30 g.) separated in glittering colourless rhombs, m. p. 160—162°. A further quantity of less pure material was separated from the mother-liquor (Found: N, 13·6; S, 15·2. $C_{10}H_{12}ON_2S$ requires N, 13·5; S, 15·2%). The compound was obtained in similar yield by saturating the cold methyl-alcoholic solution of the nitrile with ammonia and then with hydrogen sulphide and keeping it in a sealed vessel at 40° for 5 days.

4-Methyl-2-(2′-benzamidoethyl)thiazole.—A solution of the foregoing amide (41·6 g.) in anhydrous methyl alcohol (600 c.c.) was refluxed with chloroacetone (24 c.c.) and anhydrous pyridine (32 c.c.) for 4½ hours. After standing overnight the solvent was distilled off, and the oil which separated dissolved in warm N-hydrochloric acid (300 c.c.), the solution filtered (charcoal), and the filtrate adjusted to pH 7·0 with ammonia; *4-methyl-2-(2′-benzamidoethyl)thiazole* (40 g.) separated as an oil which solidified on scratching and freezing. The compound was obtained in slender colourless needles, m. p. 74—76°, by dissolution in warm benzene–ligroin and allowing the solvent to evaporate slowly in a current of cold filtered air (Found: C, 64·0; H, 5·9; N, 11·8; S, 13·6. $C_{13}H_{14}ON_2S$ requires C, 63·5; H, 5·7; N, 11·4; S, 13·0%).

4-Methyl-2-(2′-aminoethyl)thiazole.—The foregoing crude benzamido-compound (32 g.) was refluxed for 4 hours with 5N-hydrochloric acid (260 c.c.), the solution chilled, and the precipitated benzoic acid removed. The filtrate was evaporated to small volume, chilled, strongly basified with 10N-sodium hydroxide, and extracted several times with ether; the ethereal solution after drying over potassium carbonate yielded *4-methyl-2-(2′-aminoethyl)thiazole* (15 g.) as a colourless oil, b. p. 102—104°/10 mm. (Found: N, 19·6; S, 22·2. $C_6H_{10}N_2S$ requires N, 19·7; S, 22·5%).

4-Methyl-2-(2′-sulphanilamidoethyl)thiazole (No. 1323).—A solution of acetylsulphanilyl chloride (17 g.) in acetone (50 c.c.) was added dropwise during 45 minutes to a mixture of 4-methyl-2-(2′-aminoethyl)-thiazole (10 g.), sodium hydrogen carbonate (10 g.), water (150 c.c.), and acetone (20 c.c.) stirred at 10—15°. Stirring was continued at 20° for a further 4 hours, water (150 c.c.) added, and the precipitate of *4-methyl-2-(2′-acetylsulphanilamidoethyl)thiazole* (26 g.; m. p. 110°) collected and washed with water. The compound is insoluble in cold water but easily soluble in cold dilute hydrochloric acid and dilute sodium hydroxide. A sample crystallised from dilute alcohol in colourless needles, m. p. 116—118° (Found, in material dried at 1 mm. over phosphoric oxide: N, 12·3; S, 18·7. $C_{14}H_{17}O_3N_3S_2$ requires N, 12·4; S, 18·9%).

A solution of the foregoing crude acetamido-compound (20 g.) in 2·5N-sodium hydroxide (200 c.c.) was heated on the water-bath for 75 minutes. 10N-Hydrochloric acid (70 c.c.) was added, the solution filtered (charcoal), cooled, and adjusted with simultaneous scratching to pH 6·6—7·0 with dilute sodium hydroxide; *4-methyl-2-(2′-sulphanilamidoethyl)thiazole* separated in small colourless crystals (15·8 g.; m. p. 92°), which crystallised from dilute methyl alcohol in elongated needles, m. p. 98—100° (Found, in material dried over phosphoric oxide at 1 mm.: N, 14·4; S, 21·4. $C_{12}H_{15}O_2N_3S_2$ requires N, 14·2; S, 21·6%). The compound is considerably more soluble in cold 5% lactic acid than is sulphathiazole.

β-Benzamidopropionamidine Hydrochloride.—A solution of β-benzamidopropionitrile (35 g.) in anhydrous chloroform (300 c.c.) and anhydrous ethyl alcohol (46 c.c.) was saturated at 5° with dry hydrogen chloride and set aside for 18—24 hours at 0—4°. The solvent was completely pumped off at 20°, and the glittering crystalline residue of β-benzamidopropionimino-ether hydrochloride was mixed with cold anhydrous ethyl alcohol (400 c.c.) and saturated with dry ammonia at 5°. The clear solution which resulted was allowed to stand at 5° for 24—30 hours, the ammonia pumped off at 20°, the volume made up to 400 c.c. with lime-dried alcohol, and the solution filtered at the b. p. to remove ammonium chloride and kept on ice; *β-benzamidopropionamidine hydrochloride* separated in large colourless transparent cubes (34 g.; m. p. 174—180°) which were collected and dried in a vacuum. From the mother-liquors a further 7 g. (m. p. 178—180°) was obtained by evaporation. A sample recrystallised from anhydrous ethyl alcohol had m. p. 178—180° (Found: N, 18·4; Cl, 16·4. $C_{10}H_{14}ON_3Cl$ requires N, 18·4; Cl, 15·6%).

All attempts to condense this amidine with acetylacetone (i) in dilute alcohol in presence of sodium carbonate at the b. p., (ii) in refluxing anhydrous alcohol in presence of sodium carbonate, (iii) in warm (40°) and in refluxing anhydrous alcohol in presence of 1 mol. or 2 mols. of sodium ethoxide failed to yield any of the required pyrimidine. In (i) a quantitative yield of *β-benzamidopropionamide* was obtained which crystallised from boiling water in heavy colourless prisms, m. p. 174—176° (Found: C, 62·2; H, 6·3; N, 14·6. $C_{10}H_{12}O_2N_2$ requires C, 62·6; H, 6·3; N, 14·6%).

γ-Phthalimidothiobutyramide.—A mixture of 3-phthalimidopropyl cyanide (20 g.) and freshly prepared methanolic ammonium sulphide (5 g. of ammonia and 12 g. of hydrogen sulphide in 120 c.c. of methyl alcohol) was kept at 40° in a closed vessel with frequent shaking for 48 hours. The mixture was chilled, and the precipitated *amide* (11·5 g.; m. p. 184°) collected; on re-heating the filtrate to 40—45° for 5 days, a further quantity (2 g.) separated. For analysis a sample was recrystallised from alcohol and obtained in colourless needles, m. p. 186° (Found: N, 11·3; S, 13·2. $C_{12}H_{12}O_2N_2S$ requires N, 11·3; S, 12·9%).

4-Methyl-2-(3′-aminopropyl)thiazole.—The above amide (10 g.), chloroacetone (5·6 g.), pyridine (6·5 c.c.), and methyl alcohol (70 c.c.) were refluxed together for 2 hours, the solvent distilled off, and the residue diluted with water. The oil which separated slowly solidified to a crystalline mass (11·2 g.) of

4-methyl-2-(3′-phthalimidopropyl)thiazole, which crystallised from aqueous methyl alcohol in colourless prisms, m. p. 80° (Found: N, 10·0; S, 11·4. $C_{15}H_{14}O_2N_2S$ requires N, 9·8; S, 11·2%).

The foregoing compound (45 g.) was refluxed with 10N-hydrochloric acid (340 c.c.) for 8 hours, the mixture chilled, the phthalic acid removed, and the filtrate evaporated almost to dryness at reduced pressure. Basification of the residue with 10N-sodium hydroxide and extraction with chloroform yielded *4-methyl-2-(3′-aminopropyl)thiazole*, which distilled as a colourless oil (19·5 g.), b. p. 120—122°/12 mm. (Found, in redistilled sample: N, 17·8; S, 21·2. $C_7H_{12}N_2S$ requires N, 17·9; S, 20·5%).

4-Methyl-2-(3′-sulphanilamidopropyl)thiazole (No. 1432).—Acetylsulphanilyl chloride (5 g.) was added to a rapidly stirred solution of 4-methyl-2-(3′-aminopropyl)thiazole (3 g.) and sodium hydrogen carbonate (3 g.) in 50% aqueous acetone (25 c.c.), and the mixture stirred for ½ hour at room temperature and then for a further ½ hour at 50—60°. Addition of water precipitated *4-methyl-2-(3′-acetylsulphanilamidopropyl)thiazole* (6·2 g.), which crystallised from aqueous methyl alcohol in colourless prisms, m. p. 91° (Found: N, 11·8; S, 17·3. $C_{15}H_{19}O_3N_3S_2$ requires N, 11·9; S, 16·9%). Deacetylation with 2·5N-sodium hydroxide at 100° for 1 hour yielded *4-methyl-2-(3′-sulphanilamidopropyl)thiazole*, which separated from aqueous methyl alcohol in colourless needles, m. p. 130—132° (Found: N, 13·8; S, 20·5. $C_{13}H_{17}O_2N_3S_2$ requires N, 13·5; S, 20·6%).

γ-Phthalimidobutyramidine Hydrochloride.—A solution of 3-phthalimidopropyl cyanide (20 g.) in dry chloroform (100 c.c.) and anhydrous alcohol (22 c.c.) was saturated at 5° with dry hydrogen chloride and kept overnight at 5°. The solvent was completely removed at 30° under reduced pressure, anhydrous alcohol (120 c.c.) added, and the solution saturated at 5° with dry ammonia. After standing at 0—5° for 72 hours, the solvent and excess ammonia were distilled away at < 30°; crystallisation of the residue from a small volume of water yielded *γ-phthalimidobutyramidine hydrochloride* (12 g.) in colourless nacreous plates, m. p. 180—182°; for analysis a sample was recrystallised from alcohol–ether and obtained in colourless plates, m. p. 186° (Found: N, 16·1; Cl, 14·0. $C_{12}H_{13}O_2N_3$,HCl requires N, 15·7; C., 13·3%). Attempts to condense this compound with acetylacetone failed to yield any of the desired pyrimidine.

5-Benzamidothiohexoamide.—A solution of 5-benzamido-*n*-amyl cyanide (4 g.) in methyl alcohol (24 c.c.) was saturated with ammonia and then with hydrogen sulphide at 0° and kept in a closed vessel at 50° for 72 hours. Addition of a small amount of water effected separation of the *hexoamide* (1·25 g.; m. p. 90°), which crystallised from aqueous methyl alcohol in colourless leaves, m. p. 94—96° (Found: N, 11·4; S, 12·4. $C_{13}H_{18}ON_2S$ requires N, 11·2; S, 12·8%).

Use of ethanolamine or of sodium or potassium ethoxide as catalyst failed to improve the yield, and accordingly the attempt to prepare the corresponding thiazole derivative was abandoned.

5-Benzamido-n-hexoamidine Hydrochloride.—A solution of 5-benzamido-*n*-amyl cyanide (10 g.) in chloroform (60 c.c.) and ethyl alcohol (10 c.c.) was saturated at 5° with dry hydrogen chloride, kept at 5° for 24 hours, and evaporated to dryness at *ca.* 20°, and anhydrous alcohol (50 c.c.), which had previously been saturated at 0° with ammonia, was added. After standing at 5° for 72 hours and then for a further 24 hours at room temperature, a portion of the alcohol was distilled off at reduced pressure, and the residue diluted with dry ether. The oil which separated slowly solidified to a crystalline mass of the *hydrochloride* (11·5 g.; m. p. 130°); crystallisation from alcohol–ether yielded white prisms, m. p. 132° (Found: N, 15·1; Cl, 13·7. $C_{13}H_{19}ON_3$,HCl requires N, 15·6; Cl, 13·2%). All attempts to obtain a pyrimidine derivative by condensation with acetylacetone were unsuccessful.

11-Benzamidothioundecoamide.—Hydrogen sulphide was passed into a solution of 10-benzamidodecyl cyanide (25 g.) in methyl alcohol (125 c.c.) and aqueous ammonia (*d* 0·880; 20 c.c.) until an increase in weight of 10 g. was obtained. The solution was heated in a closed vessel for 7 days at 35°, water (100 c.c.) added, and the precipitate collected and recrystallised from aqueous methyl alcohol, *11-benzamidothioundecoamide* (10·5 g.) separating in pale cream needles, m. p. 112° (Found: N, 8·9; S, 10·0. $C_{18}H_{28}ON_2S$ requires N, 8·7; S, 10·0%).

4-Methyl-2-(ω-aminodecyl)thiazole.—A solution of the foregoing amide (10·5 g.) in methyl alcohol (75 c.c.) and pyridine (5·4 c.c.) was refluxed with chloroacetone (4·0 c.c.) for 3 hours. The excess of solvent was distilled off, water (100 c.c.) added to the residue, and the *4-methyl-2-(ω-benzamidodecyl)thiazole* (11·5 g.; m. p. 54°) collected; this recrystallised from aqueous methyl alcohol in white plates, m. p. 58—60° (Found: C, 70·1; H, 8·5; N, 7·8; S, 8·6. $C_{21}H_{30}ON_2S$ requires C, 70·4; H, 8·4; N, 7·8; S, 9·0%).

The foregoing crude benzamido-compound (27·3 g.) was refluxed with 10N-hydrochloric acid (273 c.c.) for 12 hours, the mixture chilled, and the benzoic acid filtered off. The filtrate was evaporated to small volume at reduced pressure, diluted with water (200 c.c.), and evaporated to dryness. Addition of 5N-sodium hydroxide to the residue, followed by chloroform extraction and distillation, yielded *4-methyl-2-(ω-aminodecyl)thiazole* as a pale yellow oil (10 g.), b. p. 166—170°/0·5 mm. (Found: N, 11·0; S, 12·8. $C_{14}H_{26}N_2S$ requires N, 11·0; S, 12·6%).

4-Methyl-2-(ω-sulphanilamidodecyl)thiazole (No. 1433).—Acetylsulphanilyl chloride (3·2 g.) was added to a stirred mixture of the foregoing base (3·0 g.), sodium hydrogen carbonate (2·0 g.), and 50% aqueous acetone (20 c.c.). After being stirred for ½ hour at room temperature, the mixture was heated on the water-bath for ½ hour, diluted with water (100 c.c.), and the precipitate (5·2 g.; m. p. 102°) collected. Recrystallisation from aqueous methyl alcohol yielded *4-methyl-2-(ω-acetylsulphanilamidodecyl)thiazole* in white needles, m. p. 102—104° (Found: N, 8·9; S, 14·2. $C_{22}H_{33}O_3N_3S_2$ requires N, 9·3; S, 14·2%). Deacetylation with 2·5N-sodium hydroxide in 50% aqueous alcohol at the reflux for 1½ hours gave *4-methyl-2-(ω-sulphanilamidodecyl)thiazole*, which separated from aqueous methyl alcohol in pale cream prisms, m. p. 108° (Found: N, 10·4; S, 15·8. $C_{20}H_{31}O_2N_3S_2$ requires N, 10·3; S, 15·7%).

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256. *Application of Thallium Compounds in Organic Chemistry. Part XI.**

By R. C. Menzies.

A summary is given of earlier work on the thallium method of alkylating sugars and its more recent extensions. It is pointed out that entry of thallium into carbohydrate molecules, controlled by Purves by varying the sizes of the molecules carrying the ethoxide in solution, can also be controlled by varying the effective size of the thallium atom by anchoring it by attached alkyl groups. A case of methylation by boiling a diethylthallium derivative with methyl iodide is also described.

Alkylations by reaction between thallous compounds and alkyl iodides were first described by Fear and Menzies (*J.*, 1926, 937), *o*-methoxybenzaldehyde, dimethyl hydroxymethoxysuccinate, and a mixture of trimethyl methylglucosides being obtained from thallous salicylaldehyde, tetrathallium tartrate, and trithallium methylglucoside. Twelve years later Purves and Hudson (*J. Amer. Chem. Soc.*, 1937, **59**, 49) methylated by this method α-methyl- and α-benzyl-fructofuranosides, both obtained by them from the uncrystallised mixture of isomeric methylfructofuranosides first prepared by the author (*J.*, 1922, **121**, 2238). Later, Hirst, Jones, and others (*J.*, 1938, 497; 1939, 458, 1482, 1867, 1884; 1942, 76; 1946, 506) described the thallation and initial methylation of an arabo-pectic acid complex and a number of vegetable gums, thus altering their solubilities so that methylation could be completed by Purdie's reaction. Hirst and Jones also showed (*J.*, 1938, 1695) that the action of methyl iodide on trithallium methylglucoside gave a mixture of 50% of 2 : 4 : 6-, 36% of 2 : 3 : 6-, 10% of 3 : 4 : 6-, and 4% of 2 : 3 : 4-trimethyl methylglucosides, so that positions 2, 3, 4, and 6 were methylated in 90, 50, 64, and 96% respectively of the whole product, positions 2 and 6 being methylated simultaneously in 86%, but positions 3 and 4 were only methylated together to the extent of 14%.

Purves later (*J. Amer. Chem. Soc.*, 1944, **66**, 59) investigated the distribution of amorphous and crystalline material in cellulose by treating it with thallous ethoxide dissolved in organic solvents of different molecular sizes.

Thallation followed by treatment with methyl iodide thus affords a method of initial partial methylation capable of being used in non-aqueous solvents, occasionally applicable where sodium hydroxide and methyl sulphate are ineffectual. Purves and Hudson's preparation of dimethyl methyl- and benzyl-fructosides and Hirst and Jones's preparation of partly methylated methylglucosides indicate that thallation can be controlled and used in the preparation of partly methylated sugars.

These authors have laid stress on results rather than on experimental methods. A recapitulation and extension of published and unpublished observations on the thallous derivatives of some of the more simple sugars and allied substances may therefore be of use.

Treatment of substances containing carboxyl or hydroxyl groups with aqueous thallous hydroxide generally results in replacement of the labile hydrogen by the metal. Where hydroxyl hydrogen is replaced, the metal can be accurately titrated with standard acid; it is also converted into thallous carbonate by passing carbon dioxide through the solution. The first compound described in which both replacements occur in the same molecule was tetrathallium tartrate (Part II). Hexathallium gluconate in which five of the six metallic atoms can be titrated was described in Part IV. *Tetrathallium* meso*tartrate*, *dithallium glycollate*, and *dithallium lactate* are described below. *Trithallium glycerol* and *tetrathallium erythritol* are both sparingly soluble, separating slowly on mixing solutions of the parent compound with aqueous thallous hydroxide. Hexathallium sorbitol was described in Part IV. Many of these and other thallium compounds crystallise well (cf. *Nature*, 1931, 907) so the recognisable patterns formed by mixing drops of the reacting solutions or on allowing their hot solutions to cool on a microscope slide are suitable for identification purposes. So far as is known all hydroxyl hydrogen atoms in straight-chain compounds can be substituted by the metal. When, however, the compound contains a pyranose, furanose, or an attached benzene ring, substitution may be incomplete. For instance, methylarabinoside (Part IV) gives a trithallium derivative, but so, under similar conditions, does methylglucoside (Part III). Sucrose, with eight hydroxyl groups, and salicin, with five, give *tetrathallium sucrose* and *trithallium salicin*. It is only in

* Previous parts of this series published in the *Journal* are: I, 1924, **125**, 1148; II, 1925, **127**, 2369; III, 1926, 937; IV, 1928, 186; V, 1930, 1571; VI, 1931, 2239; VII, 1932, 2604; VIII, 1932, 2734; IX, 1933, 21; X, 1936, 1678.

rings containing an oxygen atom that incomplete thallation has been observed. Inositol, in which all six hydroxyl groups are secondary, forms sparingly soluble ***hexathallium inositol.***

Replacement of hydrogen by the metal in certain cases is thus incomplete. Incomplete also may be subsequent replacement of the metal on treatment with methyl iodide. The attempted methylation of tetrathallium tartrate gave, for instance, after 100 hours, a syrup whose methoxyl content indicated that only three of the metallic atoms had reacted (Part III).

The isolation of well-defined thallous derivatives recalls McKenzie's suggestion (*J.*, 1899, **75**, 765) that a possible explanation of methylation by the silver oxide method is the intermediate formation of an unstable silver derivative which subsequently undergoes double decomposition with the alkyl halide (see also Lander, *J.*, 1900, **77**, 747; 1903, **83**, 416); but these intermediate compounds have never been isolated. Many of the thallous compounds are somewhat unstable, but the fact that they can be isolated facilitates more detailed examination of the mechanism of methylation. Both the occasional incomplete thallation and the usual incomplete subsequent methylation are probably partly due to steric hindrance, but this cause does not act alone. There are also to be considered the alkalinity of the metal or organo-metallic group, the dissociation constant of each individual labile hydrogen, the co-ordinating capacity of the metal, and the presence or absence of water, small amounts being occasionally of importance. Information on the above, and reciprocally, on the properties of the sugars, can be obtained by considering the courses of different methods of substitution on the same, and of the same method on different, hydroxyl compounds.

Steric hindrance certainly plays a part. Purves, for instance, has shown that the depth of entry of thallous ethoxide into fibres of cellulose depends, in the case of the ethers, on the lengths of the carbon chains attached to the oxygen of the ethers. Maxted (*J.*, 1937, 1004) showed that the catalytic activity of platinum in hydrogenations is inhibited by alkyl sulphides in proportion to the lengths of the carbon chains attached to the sulphur. The alkyl groups act like umbrellas. Similar protection of derivatives of β-diketones from hydrolysis, increasing with the length of the alkyl groups attached to the metal, was described in Part X (*loc. cit.*, p. 1880). The probable similar mechanism in this case also is made clear by Powell and Crowfoot's observation (*Z. Krist.*, 1934, **87**, 370) that the alkyl groups in the dialkylthallous compounds are attached at an angle of 180°. The effective size of the thallous atom may thus be increased in a known way without destroying, but not without altering, its power of replacing labile hydrogen, Berry, Lowry, and Gilbert (*J.*, 1928, 1761) having shown that the dialkylthallonium ions are derived from relatively weak bases. One dialkylthallium group probably does not differ much from another in basicity, so that differences between homologous organometallic derivatives may be mainly of steric origin. The non-alkylated metal, however, is a stronger base. It is shown below that in alkaline solutions, where all four labile hydrogen atoms of tartaric acid are replaced by the metal, only three are replaced by the dialkylthallium group. This difference is probably due to both the two causes indicated above. Both causes are also probably concerned in Brady and Hughes's results. They described both mono- and di-thalliumdiphenol, but only mono(diethylthallium)diphenol (*J.*, 1933, 1228). Whatever the cause and whatever alkylation method be used, it is always the insertion of the last group that is the most difficult. Even the silver oxide method occasionally breaks down. Purdie and Young, for instance (*J.*, 1910, **97**, 1524), found that the 3 : 4-dimethyl ether of 2 : 5-dimethylhexane-2 : 3 : 4 : 5-tetraol resisted methylation in this way. McKenzie and Wren (*J.*, 1910, **97**, 473) could only methylate the secondary hydroxyl group of triphenylethylene glycol by its means. Other methods break down more easily. Both the methyl sulphate (Haworth, *J.*, 1915, **107**, 15) and the thallium method (Part III) give incomplete methylation when applied to tartaric acid; and Schlubach and Firgau (*Ber.*, 1926, **59**, 2100) found that, although the potassium salt of 2 : 3 : 6-trimethyl β-methylglucoside gave an 86% yield of tetramethyl β-methylglucoside on treatment with methyl iodide, yet it was unaffected by propyl iodide, benzyl chloride, or acetobromoglucose. The smaller the metal atom or the entering group, and the looser the structure of the metallic derivative, as in Hirst and Jones's preparations of partly methylated methylglucosides and methylarabinosides referred to above, or in Percival's preparation of acetylated trimethyl sucrose (*J.*, 1935, 648), the more likely is substitution of the metal to be complete.

With regard to the varying dissociation of hydrogen from one sugar to another, it is difficult to explain that while the thallation of hexahydroxy-alcohols takes place instantly, that of glycerol and of erythritol takes hours, the solubilities of the resulting thallated derivatives being of the same order, on any other ground than that the lower alcohols must have smaller dissociation constants.

It will also be recalled that the silver oxide method began from following up Purdie and

Pitkeathly's observation (*J.*, 1899, **75**, 153) that in the course of preparation of esters by the action of alkyl halides on silver salts certain anomalous results were encountered, the tartaric esters obtained having abnormally high rotations, and it was ascertained that alkoxy-derivatives were produced during the reaction; *i.e.*, the substitution of silver, known to have a high capacity for forming co-ordination compounds, took place not only on the acid but also on the neighbouring hydroxyl group. This makes it difficult to believe, without further proof, that the replacement of thallium, also a readily co-ordinating element, by other groups always takes place on the same oxygen atom as that to which the metal was attached before reaction with the alkylating agent.

The incomplete thallation referred to above varies in some cases with quite small differences in the conditions of preparation, so that exact repetition of analytical results is occasionally difficult. This difficulty was encountered by Assat, Haas, and Purves (*J. Amer. Chem. Soc.*, 1944, **66**, 61). It is also met with in the analyses of derivatives of sucrose and cellulose and in those of ethylene glycol and of pentaerythritol. In the last two cases the solubility of the derivatives is of the same order as that of thallous hydroxide, and the analyses suggest that both the derivatives of the polyhydric primary alcohols and thallous hydroxide crystallise together. It is important to make clear that these analytical inexactitudes are due, not to the difficulty of determining the metal or of determining carbon or hydrogen in its presence, but, as explained below, to the reactive nature of the components of the molecule of which it now forms a part. Inspection of the analytical results given below and in the earlier numbers of this series will show that: (1) Carbon and hydrogen estimations are not interfered with by the presence of thallium. (2) Thallous salts of organic acids analyse well: occasional high hydrogen values suggest the presence of water of crystallisation. (3) The hydrogen values for chelate thallous compounds are usually good, but irregular carbon figures suggest the presence of thallous salts resulting from hydrolysis. (4) The percentages found for all three elements in chelate compounds of dialkylthallium are usually very good. This is associated with considerable stability. Like platinum catalyst poisons after Maxted has rendered them harmless (*J.*, 1940, 252), all the electronic shells round all the constituent atoms have been completed, and they no longer attract or are attracted by other molecules as much as those in which this is not the case. This is *mutatis mutandis* the Cambridge conception of the survival of the unattractive (Thomson, *Phil. Mag.*, 1921, **41**, 530) and their stability clearly marks the end-points of the reactions leading to their formation. This is, however, not so well marked with the thallous derivatives of the sugars. The sugars are easily oxidised, and univalent thallium is not only easily reduced to the metal but is also easily oxidised to the tervalent state, and is thus an oxygen carrier. Any thallous derivative of the sugars is thus liable to change, and it may change, if care be not taken, under the conditions of preparation. This instability makes them difficult to analyse as accurately as might be wished, but it also makes them useful synthetic agents.

Experimental.

Thallous Derivatives of Hydroxy-acids.—On adding N-thallous or -potassium hydroxide to N-solutions of tartaric or *meso*tartaric acid, the precipitation of the acid salt followed by the formation of the normal salt, which dissolves, follows the same course with both alkalis up to the point of neutrality (phenolphthalein). Here the resemblance ends. The first drop of thallous hydroxide in excess leads to precipitation of tetrathallium tartrate (Part II) or of *tetrathallium* meso*tartrate*, heavy white compact crystals, sparingly soluble and slowly darkened by light [Found: Tl (by titration), 42·41. $C_4H_2O_6Tl_4$ requires Tl, 41·14%].

A few analyses of known thallous tartrates and salts of other carbon acids are here given to illustrate the accuracy to be expected:

	Found.			Calc.		
	C, %.	H, %.	Tl, %.	C, %.	H, %.	Tl, %.
Thallous hydrogen *meso*tartrate, $C_4H_3O_6Tl$	13·9	1·7	—	13·6	1·4	—
Thallous tartrate, $C_4H_4O_6Tl_2$	8·9	0·85	73·2	8·6	0·7	73·4
Tetrathallium tartrate, $C_4H_2O_6Tl_4$	5·06	0·4	42·65 * 84·6 †	5·0	0·2	42·4 * 84·9 †
Thallous carbonate, Tl_2CO_3:						
(commercial sample)	2·76	0·24	87·3	2·51	0	87·2
(recrystallised).....	2·78	0·19	—	,,	,,	—
Thallous formate, CHO_2Tl	4·9	0·8	82·15	4·8	0·4	81·95
Thallous fumarate } $C_2H_2O_4Tl_2$	9·3	0·56	77·9 }	9·2	0·4	78·2
Thallous maleate }	9·4	0·4	77·8 }			
Thallous succinate, $C_4H_4O_4Tl_2$	9·2	0·85	77·6	9·16	0·76	77·9

* By titration. † As iodide.

Although these results conform to the usually accepted standards of accuracy, it will be seen that where the molecular weights of normal and tetrathallium tartrates, for instance, are 556·8 and 963·6 respectively, they are inadequate to indicate the presence or absence of small quantities of water of crystallisation, probably influencing, as mentioned above, the course of alkylations. It may be mentioned in this connection that thallium hydrogen *d*-tartrate is described in the literature as anhydrous, while the *meso*tartrate is said to crystallise as a hemihydrate. In alkaline solution the behaviour of the metal resembles that of lead and antimony. The resemblance between tetrathallium and a double tartrate of thallium and antimony has already been pointed out in Part II (p. 2369), and comparison may also be made with a basic lead tartrate $Pb_2C_4H_2O_6,H_2O$ (Beilstein's " Handbuch ", Vol. 3, p. 501).

Dithallium glycollate. Glycollic acid was neutralised by thallous hydroxide solution, and a further equal volume was then added. Compact colourless crystals of *dithallium glycollate* slowly separated, resembling, but more soluble than, tetrathallium tartrates, and like them, darkened by light [Found : Tl (by titration), 42·1. $C_2H_3O_3Tl_2$ requires Tl, 42·4%].

From a solution of glycollic acid accurately neutralised with thallous hydroxide (phenolphthalein) were obtained on evaporation needles of the very soluble normal salt described by Fahlberg (*J. pr. Chem.*, 1873, **7**, 339). From a solution of lactic acid neutralised with thallous hydroxide a colourless syrup was obtained on evaporation, which did not crystallise; but on evaporating a solution to which twice the amount of hydroxide necessary for neutralisation had been added, as above, *dithallium lactate* slowly separated on nucleation with a sample obtained by rapid evaporation in a test-tube, in large, highly refracting, colourless crystals [Found : C, 7·6, 7·8; H, 0·91, 1·03; Tl (by titration), 39·4. $C_3H_4O_3Tl_2$ requires C, 7·25; H, 0·8; Tl, 41·15. $C_3H_4O_3Tl_2,H_2O$ requires C, 7·0; H, 1·2; Tl, 39·7%].

The above basic salts are all colourless. Yellow hexathallium gluconate was described in Part III (p. 189). Saccharic acid also gives a substance approximating in composition to hexathallium saccharate, the way to which lies through *thallium hydrogen saccharate*, now described.

Crude brown potassium hydrogen saccharate (19 g.) was dissolved in water and partly neutralised with thallous hydroxide. The dark brown liquid was then boiled with animal charcoal, and considerable excess of thallous hydroxide added to the almost colourless filtrate. The solution was then made slightly acid with acetic acid, and again boiled with animal charcoal, filtered hot, and cooled. Crude thallium hydrogen saccharate (14·8 g.) separated, which probably contained a little potassium, as the titration value corresponded to 101·3% of thallium hydrogen saccharate. After recrystallation from hot water, however, 2·126 g. required 5·11 c.c. of N-thallous hydroxide (calc., 5·14 c.c.), indicating 99·4% purity (Found : C, 18·3; H, 2·3. $C_6H_3O_8Tl$ requires C, 17·4; H, 2·2%). The neutral solution obtained by titration gave a glass on evaporation to dryness, thus resembling the normal lactate and also recalling Hirst and Purves's attempt to prepare normal thallium *xylo*trimethoxyglutaric acid (*J.*, 1923, **123**, 1358). The syrup was then redissolved, and on the addition of four further equivalents of thallous hydroxide an amorphous yellow precipitate came down, more being obtained by adding alcohol to the filtrate. These on titration showed 52·24% and 50·74% of thallium, respectively. Hexathallium saccharate should contain 85·74% of thallium of which two-thirds or 57·16% should be titratable. It is possible that, on the lines indicated in Part III for the similar yellow hexathallium compounds of gluconic acid and of sorbitol, better analytical results could be obtained. But it is already evident that again the close resemblance between thallous and potassium salts in neutral or acid solutions persists. On making the solution alkaline with thallous hydroxide, more sparingly soluble substances are formed. From hydroxy-acids containing 2, 3, and 4 carbon atoms, these are colourless. From acids and alcohols containing 6 carbon atoms they are yellow. As will be seen below, this yellow colour already appears in the derivatives of ethylene glycol and of glycerol. (Solid TlOH is also yellow.)

Normal *thallous mucate* is easily prepared by neutralising the acid. It is sparingly soluble but can be crystallised from hot water. Its analysis is a good example of the general rule that the more sparingly soluble an organic thallium salt is the better does it analyse (Found: C, 11·8; H, 1·35. $C_6H_8O_8Tl_2$ requires C, 11·7; H, 1·3%).

Thallous Derivatives of Polyhydric Alcohols.—Sparingly soluble, of definite composition, yellow and darkened by light are *trithallium glycerol* and *tetrathallium erythritol*. A typical preparation is the following. Tetrathallium erythritol (51·1 g., 71·6%) crystallised after some hours' standing from a solution containing erythritol (9·3 g.), 6N-thallous formate (50 c.c.), 6N-sodium hydroxide (50 c.c.) and water (150 c.c.) (Found : C, 5·10; H, 0·76; Tl, 87·0. $C_4H_6O_4Tl_4$ requires C, 5·13; H, 0·65; Tl, 87·4%). The *glycerol* compound was prepared similarly (Found : C, 5·18; H, 0·70; Tl, 87·7. $C_3H_5O_3Tl_3$ requires C, 5·18; H, 0·72; Tl, 87·3%).

Thallium compounds of ethylene glycol. De Forcrand (*Compt. rend.*, 1923, **176**, 20) described monothallium ethylene glycol prepared from thallous ethoxide and ethylene glycol as a beautiful precipitate closely resembling dehydrated uranium nitrate. He prepared the glycerol derivative, $C_3H_5(OH)_2OTl$, similarly but did not report analyses. Chablay (*Ann. Chim.*, 1917, **8**, 185) prepared dithallium ethylene glycol from monosodium ethylene glycol and thallous nitrate, both dissolved in liquid ammonia. According to him, monothallium ethylene glycol is first formed, 2 mols. of which interact with formation of ethylene glycol and the disubstituted compound. Chablay noted that the compound is soluble in water and that the metal can be determined by titration. He also described a dithallium mannitol made in the same way. Several preparations have now been made of a yellow substance crystallising from weighed quantities of ethylene glycol dissolved in equivalent amounts of aqueous thallous hydroxide. From 2N-solutions yellow crystals were obtained, the mother-liquor from which was 0·92N at room temperature. Analyses indicated that they were a mixture of approximately 2 mols. of dithallium ethylene glycol with 1 mol. of thallous hydroxide [Found : C, 4·14, 4·00, 3·80; H, 0·95, 0·94, 0·85; Tl, 87·7, 88·7. Calc. for $C_2H_4O_2Tl_2$: C, 5·12; H, 0·86; Tl, 87·2. Calc. for TlOH : C, 0; H, 0·45; Tl, 92·3. Calc. for $2(C_2H_4O_2Tl_2),TlOH$: C, 4·17; H, 0·79; Tl, 88·9. Calc. for $2(C_2H_4O_2Tl_2),TlOH,H_2O$: C, 4·11; H, 0·95; Tl, 87·5%].

Similar results were obtained with pentaerythritol. This alcohol (6 g.) was dissolved in water (20 c.c.) and filtered hot, and thallous ethoxide (44·6 g.; 1 equiv. for each hydroxyl group) was also dissolved in water (60 c.c.), boiled, and filtered hot; on being mixed, the solution became yellow, and, on cooling,

crystals having the appearance of those of thallous hydroxide separated. The whole was then boiled down to half bulk. On cooling, a heavy, yellow, sandy powder separated which adhered firmly to the sides of the flask. This was separated with some difficulty and filtered through a weighed Gooch crucible, washed with alcohol and ether, and dried in a vacuum over phosphoric oxide for 24 hours (Substance *A*; 18·65 g.) (Found: C, 4·67; H, 0·9; Tl 86·96. Calc. for $C_5H_8O_4Tl_4$: C, 6·32; H, 0·85; Tl, 86·1. Calc. for $C_5H_8O_4Tl_4,TlOH,H_2O$: C, 5·05; H, 0·93; Tl, 86·0%). A further 8·5 g. were similarly obtained by adding alcohol to the filtrate (Substance *B*) [Found: C, 4·82; H, 0·93; Tl (titration), 86·09; Tl (iodide), 87·65%]. The substance obtained from ethylene glycol is thus slightly less soluble than thallous hydroxide, and that from pentaerythritol slightly more soluble. All three solubilities are of the same order, and both alcoholic derivatives appear to form mixed crystals with the hydroxide.

Dithallium trimethylene glycol (23 g.; 95·3%) was obtained as a light yellow precipitate on adding thallous ethoxide (25 g.) in ether to trimethylene glycol (3·8 g.). It was soluble in water but not in benzene (Found: C, 7·61; H, 1·50; Tl, 84·2. $C_3H_6O_2Tl_2$ requires C, 7·46; H, 1·25; Tl, 84·7%).

The thallous derivatives of the hexahydric alcohols resemble those of the di-, tri-, and tetra-hydric alcohols in being yellow and coloured more deeply by light. They differ from them in that they are precipitated instantly on mixing the respective solutions and in being amorphous.

From mixed 2N-solutions containing approximately 1 equiv. of thallous hydroxide for each hydroxyl group of inositol (m. p. 225°) a heavy yellow precipitate of *hexathallium inositol* was obtained [Found: Tl (titration), 87·36. $C_6H_6O_6Tl_6$ requires Tl, 87·6%. $C_6H_7O_6Tl_5$ requires Tl, 85·37%. $C_6H_8O_6Tl_4$ requires Tl, 82·11%]. On adding a slight excess of N-sodium hydroxide to the solution resulting from the above titration a similar yellow solid separated [Found: Tl (titration), 83·5%]. From N-solution the replacement of hydrogen by thallium is not so complete (Found, for precipitate from inositol and 1·1 equivs. of TlOH for each hydroxyl group: C, 5·62; H, 0·58; Tl, 85·75. $C_6H_6O_6Tl_6$ requires C, 56·14; H, 0·43; Tl, 87·6%. $C_6H_7O_6Tl_5$ requires C, 6·01; H, 0·58; Tl, 85·37%).

Inositol has no terminal groups which can be oxidised, and of 0·0298 equiv. of thallous hydroxide taken in this last experiment 0·0297 equiv. was accounted for by titration of the solid and of the mother-liquor. In a comparative experiment using glucose and working in the cold, 7·4% of the titratable thallium disappeared, having been neutralised by acid products of oxidation.

From mannitol and dulcitol and 1 equiv. of thallous hydroxide for each hydroxyl group in approximately 1·3N-solution, yellow *derivatives* were obtained containing 85·94 and 84·05% thallium respectively by titration ($C_6H_9O_6Tl_6$, $C_6H_9O_6Tl_5$, and $C_6H_{10}O_6Tl_4$ require respectively Tl, 87·45, 85·23, and 82·11%). The dulcitol compound is coloured brown by light: the inositol compound is turned black. Of the three, the mannitol compound is least changed in colour by light.

The above observations suggest that the thallous derivatives of secondary polyhydric alcohols tend to be less soluble than those of primary, that in the more sparingly soluble derivatives replacement of hydroxyl hydrogen by the metal occurs, but that in cases where the solubility is of the same order as that of the hydroxide addition of thallous hydroxide and of water also takes place. In addition to this, as pointed out on p. 1378, complete substitution of hydrogen by the metal does not always occur from aqueous solutions in more complicated molecules. The derivatives of sucrose, a disaccharide containing eight hydroxyl groups, of which three are primary, and of salicin, a phenolic glucoside containing five hydroxyl groups of which two are primary, are now discussed in the light of the above remarks.

(i) A typical preparation of the *thallous* derivative of sucrose is the following. Sucrose (8·8 g.) was dissolved in water (8 c.c.), cooled, and mixed with 1·275N-aqueous thallous hydroxide solution (68·5 c.c.), *i.e.*, 5 equivs. per mol. of sucrose. After about 2 minutes the mixture became cloudy, and after an hour the white solid separating was filtered off at the pump and kept on a tile in a vacuum over sulphuric acid, taking 4 days to attain constant weight (22·5 g.) [Found: Tl (titration), 70·7; Tl (as iodide), 71·6. $C_{12}H_{18}O_{11}Tl_4$ requires Tl, 70·7%]. On drying, the solid turned yellow. A sample of thallous hydroxide placed in a dry tube at 100° turns black owing to formation of thallous oxide (Tl_2O), whilst the colour of the sucrose compound is unchanged by this treatment.

Preparations carried out with 4 equivs. of the hydroxide to one of sucrose gave substances of similar appearance but of slightly lower thallium content. For instance, 284·6 g. (yield 71·7%) [Found: Tl (titration), 69·9; Tl (as iodide), 68·7%] were obtained from 117·4 g. of sucrose and 4 equivs. of 1·26N-thallous hydroxide. Higher proportions of the hydroxide did not give rise to a corresponding increase of the thallium content, for on treating sucrose with 8 equivs. followed by slow evaporation in a vacuum the first crop separating contained 71·2% of thallium, determined as iodide. The carbon percentages, however, were low and those for hydrogen high. A nearer approach to the observed percentages is afforded by the formula $(C_{12}H_{19}O_{11}Tl_3)_2,3TlOH,H_2O$ or $(C_{12}H_{18}O_{11}Tl_4)_2,TlOH,3H_2O$, both adding up to $C_{24}H_{43}O_{24}Tl_9$ which requires C, 11·13; H, 1·67; Tl, 71·5% (Found, for two typical samples: C, 11·14, 11·57; H, 1·98, 1·78; Tl, 70·7, 71·6%) and both similar to the results found for the derivatives of ethylene glycol and pentaerythritol.

It is of interest to compare these results with those of Mackenzie and Quin (*J.*, 1929, 951) and of Percival (*J.*, 1935, 648).

(ii) Salicin (3 g.) and thallium hydroxide crystals (9 g.; 3·9 equivs.) were dissolved separately in water, and the solutions mixed and heated; on cooling and addition of alcohol, 7·5 g. of a light yellow *substance* separated (Found: C, 17·27; H, 1·99; Tl, 64·2%). On evaporation of the solution in a vacuum desiccator, white crystals separated which turned yellow on drying (Found: C, 17·27; H, 1·92; Tl, 63·6%). The mother-liquor yielded a white precipitate on addition of alcohol. These also turned yellow on drying (Found: C, 16·67; H, 1·94; Tl, 63·2. $C_{13}H_{15}O_7Tl_3$ requires C, 17·4; H, 1·65; Tl, 68·4%. $C_{13}H_{15}O_7Tl_3,2H_2O$ requires C, 16·73; H, 2·05; Tl, 65·8%).

Surgical cotton-wool (1·71 g., dried over phosphoric oxide. Found: C, 42·7; H, 6·18. Calc. for cellulose: C, 44·44; H, 6·18%) was placed in 1·52N-thallous hydroxide solution and left for 24 hours. The product was then washed repeatedly with alcohol, which converts excess thallous hydroxide into the ethoxide which then dissolves in the alcohol. The product was unchanged in appearance but became yellow on drying, when it weighed 8·24 g. [Found: C, 9·58; H, 1·41; Tl (titration), 73·1;

Tl (as iodide), 75·3%]. In another experiment 4·35 g. of the same cotton-wool were boiled with 1·52N-thallous hydroxide for 15 minutes, washed with alcohol, and dried as before. The dried product weighed 17·36 g. [Found: C, 11·29; H, 1·67; Tl (titration), 63·5; Tl (as iodide), 72·4. Dithallium cellulose requires C, 12·66; H, 1·41; Tl, 71·86%. Trithallium cellulose requires C, 9·32; H, 0·91; Tl, 79·41%. $(C_6H_8O_5Tl_2)_2,TlOH,2H_2O$ requires C, 10·3; H, 1·52; Tl, 73·25%]. In view of the uncertain composition of the cotton-wool used, these results cannot be considered as more than indicating a possible point of departure with pure cellulose should this ever prove to be obtainable.

The basic thallous compounds described above are to be classified as salts, for they are, in the main, insoluble in non-hydrolytic solvents and soluble in water; they are also likely to char on heating without melting (cf. Sidgwick and Brewer, *J.*, 1925, **127**, 2379). Thallous methoxide is intermediate. The thallous derivatives of the other normal primary alcohols have definite m. p.s and are more soluble in organic solvents than in water. The basic salts described, however, do resemble many chelate compounds in being stable to alkalis. This property is shared by acetals, and, as was described in Part X, several of the dialkylthallium derivatives of β-diketones are volatile in steam from alkaline solutions. This took place much more easily with the derivatives of dipropionylmethane than with those of acetylacetone. Further, beryllium dipropionylmethane (see below) is volatile in steam in the presence of a little ammonia while beryllium acetylacetone is not. It is not clear whether these facts are really connected.

Beryllium dipropionylmethane is readily made by heating beryllia with the diketone in benzene until the distillate is clear, filtering the residue from excess of beryllia, distilling off the benzene, and finally distilling the residue in a water-pump vacuum; m. p. 63° (Found: C, 62·5; H, 8·46. Found, after distillation in steam, and drying: C, 61·9; H, 8·4. $C_{14}H_{22}O_4Be$ requires C, 63·8; H, 8·4%). It closely resembles beryllium acetylacetone, but is inconveniently soluble in ether, and is better recrystallised from ligroin. On boiling with water containing a little ammonia it distills with the steam essentially unchanged. This does not happen with beryllium acetylacetone.

Action of Air, Light, and Moisture on Thallous Derivatives of Cotton-wool, Salicin, and Sucrose. (Adapted from a report by E. R. Wiltshire.)— The observation that the yellow colour of these compounds either appeared on or was intensified by drying led to an examination of the effect of exposing them to a moist atmosphere. Light caused darkening of the first compound. The experiments were therefore carried out by leaving the substances over water in closed vessels in the dark. In each case the yellow colour was gradually lost. As many of the dialkylthallium derivatives are lighter in colour than the corresponding derivatives of the non-alkylated metal, it is reasonable to suppose that this loss of colour is due to the attachment of water to the metal. The precipitate, for example, obtained by passing hydrogen sulphide through a solution of a thallous salt is black, but a white precipitate is obtained from dialkylthallous salts. No information, however, as to the existence of definite hydrates could be obtained from the increase of weight, as the absorption of water appeared to continue indefinitely. After one month the three derivatives gained 44, 58, and 18%, respectively.

A similar experiment was then carried out with a thallium derivative of more definite composition. Thallous fumarate gained the equivalent of 1 mol. of water after 50 days and of 2 mols. after three months. Diethylthallium fumarate gained 3% in 22 days, 1 mol. of water corresponding to 2·4%. In Part II it was shown that thallous 2-methylpyridine-3 : 4 : 6-tricarboxylate gained the equivalent of 1 mol. of water in 6 days, after which the weight became constant.

Exposure of thallium derivatives to a moist atmosphere. In each case, a weighed amount of the substance was placed on a watch-glass in a receptacle containing water in the dark:

A.	Thallium cellulose.	Thallium salicin.	Thallium sucrose.
Original wt., g.	0·823	0·517	1·967
Increase after 1 month, g.	0·366	0·302	0·358
,, ,, 1 month, %	44·47	58·4	18·2

The colour in each case gradually disappeared, and finally darkening began to take place. None of the substances came to constant weight.

B.	Thallous fumarate. G.	Thallous fumarate. %	Diethylthallium fumarate. G.	Diethylthallium fumarate. %
Original weight	6·617	—	0·599	—
Increase in wt. after 20 days	0·144	2·2	0·017	3·0
,, ,, ,, 50 ,,	0·219	3·3	—	—
,, ,, ,, 3 months	0·452	5·8	—	—
Calc. for addition of 1 mol. of H_2O	—	3·45	—	2·4

Constant weight was not obtained, but in each case exposure to the atmosphere quickly caused reversion to the original weight.

Dimethyl- (Found: C, 16·32; H, 2·46. Calc. for $C_8H_{14}O_4Tl_2$: C, 16·46; H, 2·42%) and diethylthallium fumarates (Found: C, 22·58; H, 3·37. Calc. for $C_{12}H_{22}O_4Tl_2$: C, 22·6; H, 3·48%) were prepared respectively in 52 and 56% yields by double decomposition between thallous fumarate and the dialkylthallium iodide in boiling water.

The Dialkylthallium Tartrates.—These can be prepared by neutralising tartaric acid with aqueous solutions of the dialkylthallium hydroxides. 4·196 G. of tartaric acid are theoretically required to neutralise 235 c.c. of 0·238N-diethylthallium hydroxide: the weight required lay between 4·1 and 4·19 g. The solution was filtered and evaporated to small bulk on the water-bath. The compound is very soluble in water. On concentration, four crops were obtained: (1) 3·1 g., (2) 6·95 g. on concentrating the aqueous solution. On adding methyl alcohol to the filtrate from crop (2), 3·7 g. were obtained

(crop 3), and finally 2·5 g. on evaporating to dryness (crop 4). Crops 2 and 3 were analysed (Found, respectively: C, 22·4, 19·2; H, 3·17, 3·35. Calc. for $C_{12}H_{24}O_6Tl_2$: C, 21·58; H, 3·63%).

Treatment of diethylthallium tartrate with methyl iodide. 2·63 G. of the tartrate were refluxed with methyl iodide for 17 hours; on removal of the methyl iodide, extraction with ether, filtration, and evaporation of the ether, 0·48 g. of syrup was obtained together with 2·9 g. of colourless diethylthallium iodide, corresponding to 58·3% of thallium in the diethylthallium tartrate taken (Calc.: Tl, 61·3%). As this was evidence that the methylation did proceed, the preparation was then repeated with 11·7 g. of the tartrate. A syrup was obtained which was distilled in a water-pump vacuum; the distillate solidified on nucleation with an authentic sample of dimethyl tartrate (Found: C, 40·85; H, 5·72. Calc.: C, 40·45; H, 5·52%).

Dipropylthallium tartrate. This can be prepared from normal thallous tartrate and dipropylthallium bromide by boiling them together with water. The *substance* (Found: C, 27·13; H, 4·42. $C_{16}H_{32}O_6Tl_2$ requires C, 26·34; H, 4·42%) is very soluble both in water and in benzene. Probably connected with this is the fact that on evaporating an aqueous solution on a water-bath, crystallation first begins on the surface of the solution. This also takes place with solutions of diethylthallium tartrate. This surface crystallisation is also characteristic of the dialkylthallium halides, and in their case takes place in a very regular pattern (*Nature*, 1931, 907). The floating crystals are probably visible examples of McBain's ionic micelles.

Attempts to prepare tetrakis-dimethyl-and -diethyl-thallium tartrates by heating tetrathallium tartrate with the respective dialkylthallium halide resited in the formation of the trisdialkylthallium tartrates only; the incomplete substitution which appears in the thallous compounds of more complicated substances now occurs in the simple tartaric acid molecule, the effective size of the metal having been increased and its strength as an alkali reduced by alkylation.

Treatment of tetrathallium tartrate with dimethylthallium bromide. 4·82 G. (1 equiv.) of the tartrate were boiled with 6·3 g. (4 equivs.) of the bromide. The solution was cooled, filtered from thallous bromide, and concentrated to small bulk. 0·16 G. of sparingly soluble substance, probably unreacted bromide, was filtered off, and then on adding alcohol 2·4 g. of a white precipitate of *trisdimethylthallium tartrate* were obtained [Found (titration): Tl, 22·8. $C_{10}H_{21}O_6Tl_3$ requires Tl (titration), 24·0%]. Another portion, washed with alcohol and acetone and dried in a vacuum, contained Tl, 23·4% (by titration).

Treatment of tetrathallium tartrate with diethylthallium iodide. 12 G. of the tartrate were heated in water with excess of the iodide. Two crops were obtained, containing severally Tl, 20·75, 23·16% (by titration). On addition of potassium iodide to a solution, diethylthallium iodide was recovered corresponding to 66·64% of thallium [*trisdiethylthallium tartrate*, $C_{16}H_{33}O_6Tl_3$, requires Tl (total), 65·63; Tl (by titration), 21·88%].

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THE UNIVERSITIES OF BRISTOL AND EDINBURGH. [*Received, November 29th*, 1946.]

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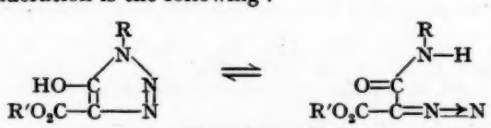
257. *The Mechanism of the Tautomeric Change of 5-Hydroxy-1 : 2 : 3-triazole-4-carboxylic Esters into Aliphatic Diazo-compounds.*

By B. R. BROWN and D. LL. HAMMICK.

Dimroth (*Annalen*, 1904, **335**, 1; 1905, **338**, 143; 1910, **373**, 336) interpreted the kinetics of this reaction as showing that the change takes place in the un-ionised enol molecule. A reconsideration of his data indicates that the change is bimolecular, involving a proton and an enol ion. The electronic processes involved in the proposed mechanism are deduced from a comparison of rate constants for various substituted triazole esters.

THE reaction under consideration is the following:



(I; R′ = Me or Et.)

which was established by Dimroth (*loc. cit.*). Owing to the fact that the enolic triazole tautomer is acidic, he was able to study the kinetics of the forward reaction and the equilibrium in various solvents. He interpreted his results as showing that the reaction is unimolecular

with respect to the enol, and concluded that the change from enol to neutral form takes place in the un-ionised enol molecule. His evidence (*Annalen*, 1904, **335**, 60) was the observed proportionality between the rate in the presence of various concentrations of the sodium salt of the enol, and the amount of undissociated enol as calculated from the " degree of dissociation " of the sodium salt obtained from conductivity data. His conclusion is invalid on account both of this fallacious " degree of dissociation ", and of the occurrence of an appreciable salt effect.

A reconsideration of Dimroth's results in the light of more recent ionic and kinetic theory shows that the reaction is in reality a bimolecular process involving a hydrogen ion and an enol ion. Thus his values (*ibid.*, p. 53) for the rate constants in the presence of water and of 0·06N-sodium chloride :

k (mins.$^{-1}$) at 50° in water (I; R = phenyl) = 0·00128
k (mins.$^{-1}$) at 50° in 0·06N-NaCl (I; R = phenyl) = 0·00106

reveal a negative salt effect and indicate that the reaction is between two oppositely charged ions. Also his unimolecular rate constants increase as the concentration of either the hydrogen ion or the enol ion increases (*ibid.*, p. 54) :

k (mins.$^{-1}$) at 50° in water (I; R = phenyl) = 0·00128
k (mins.$^{-1}$) at 50° in dilute HCl (I; R = phenyl) = 0·00195

Mols. of Na salt of enol : mols. of enol.	k (mins.$^{-1}$).
0 : 1	0·00128
1 : 1	0·00195
2 : 1	0·00225
4 : 1	0·00267
8 : 1	0·00306

Addition of alkali causes an increased rate of reaction by increasing the concentration of enol ion. This fact is remarked upon by Dimroth (*ibid.*, p. 3), and prevents an ordinary alkali titration being used to follow the reaction.

Following up this evidence, Dimroth's results (*ibid.*, p. 49) for the tautomerism of (I; R = phenyl) in water have been recalculated using a bimolecular rate equation. His values (*ibid.*, 1905, **338**, 175; 1904, **335**, 57) for the dissociation constant of this compound in water are :

K at 25° = $1·6 \times 10^{-2}$
K at 50° = $1·3 \times 10^{-2}$

whence the value at 40° is estimated at $1·4 \times 10^{-2}$. Using these dissociation constants and the following equations for the estimation of the enol,

$$6(C_{10}H_8O_2N_3)OH + 5KI + KIO_3 = 6(C_{10}H_8O_2N_3)OK + 3H_2O + 3I_2$$
$$I_2 + 2Na_2S_2O_3 = Na_2S_4O_6 + 2NaI,$$

the following typical sets of results were calculated :

25 *C.c. of reaction mixture titrated against* N/50-*thiosulphate* (*temp.*, 50°).

Time (mins.).	Titre (c.c.).	[H$^+$] = [enol ion]. (mols./l.).	Bimol. k (mols./l./sec.).	Dimroth's unimol. constant 0·4343k (mins.$^{-1}$).
0	18·55	$0·884 \times 10^{-2}$		
60	17·10	0·834 ,,	$1·88 \times 10^{-3}$	$5·89 \times 10^{-4}$
120	15·85	0·789 ,,	1·94 ,,	5·69 ,,
180	14·68	0·747 ,,	1·92 ,,	5·65 ,,
300	12·62	0·667 ,,	2·05 ,,	5·57 ,,
400	11·13	0·607 ,,	2·15 ,,	5·54 ,,
		Average :	1·99 ,,	
		Average for a similar set at 50° :	1·88 ,,	

100 *C.c. of reaction mixture titrated against* N/10-*thiosulphate* (*temp.*, 40·2°).

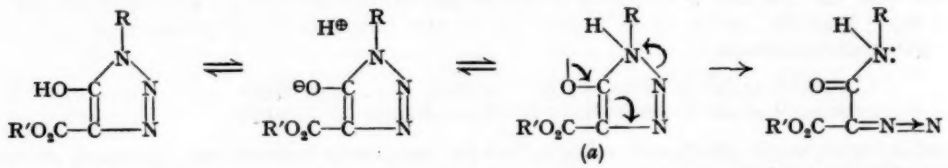
0	12·77	$0·809 \times 10^{-2}$		
170	12·13	0·779 ,,	$4·67 \times 10^{-4}$	$1·31 \times 10^{-4}$
300	11·70	0·759 ,,	4·53 ,,	1·27 ,,
380	11·47	0·748 ,,	4·46 ,,	1·23 ,,
470	11·15	0·732 ,,	4·61 ,,	1·21 ,,
		Average :	4·57 ,,	

Whence, $k_{50°} = 1{\cdot}94 \times 10^{-3}$ and $k_{40{\cdot}2°} = 4{\cdot}57 \times 10^{-4}$, both in mols./l./sec. Substitution in the equation $k = PZe^{-E/RT}$ gives the following E and PZ values :

$$E = 29{,}660 \text{ cals.} \qquad PZ = 10^{+17{\cdot}3}$$

It is seen that the PZ value is one normally observed for a reaction between oppositely charged ions, *viz.*, 10^{+13} to 10^{+19} (Bell, *J.*, 1943, 629), and therefore supports a bimolecular ionic mechanism.

These considerations lead us to suggest the following picture of the tautomeric change :

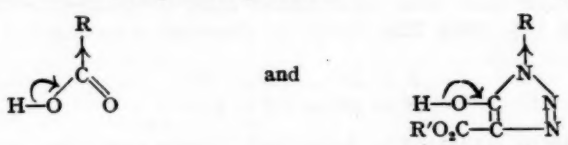


(*a*)

Evidence that the electronic processes implied in (*a*) for the decomposition of the transition state are rate-determining is obtained by a consideration of the effects of substituents on the rate constants and on the equilibrium constants. These will be expected to parallel the dissociation constants of the enol, which in turn should parallel the dissociation constants of the corresponding acids, $R{\cdot}CO_2H$. That the latter is the case is evident from Dimroth's determination of the dissociation constants of various enol forms :

R.	$R{\cdot}CO_2H$. (Watson, " Modern Theories of Organic Chemistry," 2nd Edition, 1941, p. 27.)	Enol. (Dimroth, *Annalen*, 1905, **338**, 175.)
Methyl	$1{\cdot}82 \times 10^{-5}$	$0{\cdot}3 \times 10^{-2}$
p-Tolyl	4·24 ,,	1·0 ,,
Phenyl	6·27 ,,	1·6 ,,
p-Bromophenyl	10·7 ,,	2·0 ,,

It is seen that the dissociation constants increase with the power of the group R to accept electrons, as expected for the comparable processes :



The electronic processes (*a*) in the proposed mechanism should likewise be facilitated by acceptor groups at R, and hence the rate and equilibrium constants (diazo-compound/triazole) should increase in the same order as the ionisation constants, *i.e.*, with the accepting power of R. That this does occur is good evidence for the proposed electron shifts.

Values of K *and* k *in ethyl alcohol at* 25°.

(Dimroth, *Annalen*, 1910, **373**, 349.)

R.	*K*.	*k* (mins.$^{-1}$).
Benzyl	118	$0{\cdot}003 \times 10^{-2}$
p-Tolyl	120	0·94 ,,
Phenyl	300	1·02 ,,
p-Bromophenyl	555	4·58 ,,
p-Nitrophenyl	very large	60·0 ,,
2 : 4-Dinitrophenyl	not measurable	100·0 ,,

Thus Dimroth's kinetic data indicate that the reaction has an ionic mechanism, involving the attack of a proton on an enol ion, and furthermore, enable the nature of the electronic shifts involved to be elucidated with a fair degree of certainty.

We wish to thank Mr. R. P. Bell, F.R.S., for helpful criticism.

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258. *The Absorption Spectra of 2 : 4-Dinitrophenylsemicarbazones.*

By A. E. Gillam and D. G. Moss.

The absorption spectra of new and previously-prepared 2 : 4-dinitrophenylsemicarbazones of various aldehydes and ketones are recorded and shown to be, approximately, summation curves of the light absorption due to the reagent and that of the chromophore

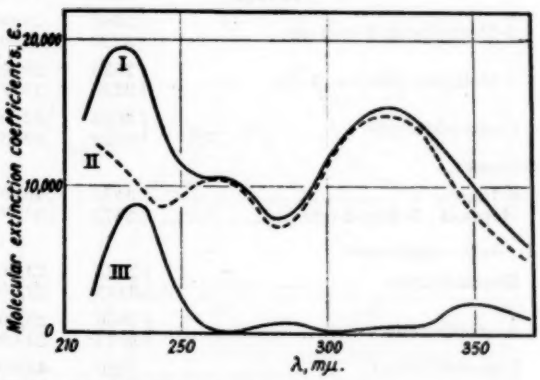
$$R—[CR'=CH]_n—CR''=N-$$

where $n = 0$, 1, 2, or 3 and R, R′, and R″ may be either H or alkyl. The maxima of the subtraction curves suffer a steady displacement to longer wave-lengths as the conjugated system is lengthened.

In earlier papers (*J.*, 1940, 1453; 1941, 815; 1943, 565; 1945, 432) light-absorption data on carbon compounds containing specific chromophoric groups such as those of unsaturated ketones and their semicarbazones and similar derivatives were collected and classified with the object, among others, of using the data in the determination of molecular structure. In the present communication the absorption spectra of 2 : 4-dinitrophenylsemicarbazones of various carbonyl compounds are recorded and an attempt is made to correlate the location of the absorption bands with the structure of the compounds and especially the length of the conjugated system present.

2 : 4-Dinitrophenylsemicarbazide was first prepared by Kniphorst (*Rec. Trav. chim.*, 1925, **44**, 724) who also showed that it formed condensation products with carbonyl compounds. McVeigh and Rose (*J.*, 1945, 713) have more recently shown that it can be used as a means of detection and characterisation of aldehydes and ketones generally, and have recorded the melting points of a number of derivatives of such compounds.

Fig. 1.



Absorption spectra in alcohol :
I. cyclo*Hexanone* 2 : 4-*dinitrophenylsemicarbazone.*
II. 2 : 4-*Dinitrophenylsemicarbazide.*
III. *Subtraction curve.*

The molecules of these carbonyl derivatives contain two main chromophoric units, namely 2 : 4-dinitrophenylsemicarbazide itself and the substituted $>C=N-$ group formed by condensation of the carbonyl group with the active $-NH_2$ group of the semicarbazide. With αβ-unsaturated ketone derivatives the chromophoric groups are those of the substituted semicarbazide itself and the $CR_2{:}CH{\cdot}CR{:}N-$ group which is, in effect, the $-\overset{|}{C}=\overset{|}{C}-\overset{|}{C}=N-$ chromophore normally met with in simple semicarbazones (cf. Evans and Gillam, *J.*, 1943, 565). The work of Ramart-Lucas and her various collaborators (*Bull. Soc. chim.*, 1932, **51**, 289) has shown that in a compound having two unconjugated chromophores the light absorption approximates more nearly to a simple summation the more widely separated are the chromophores in the molecule. Thus in the 2 : 4-dinitrophenylsemicarbazones of unsaturated carbonyl compounds the two compound chromophores are unconjugated but not widely separated so that complete independence is not to be expected.

If we compare the absorption curves of the substituted semicarbazones of simple ketones with those of the corresponding derivatives of αβ-unsaturated ketones and of dienones we would further expect to find that the summation curves contain a fixed component (the semicarbazide chromophore) and one which varies in the location of its band with the length of the conjugated system responsible for it. Thus in any observed absorption curve of a 2 : 4-dinitrophenylsemicarbazone if we subtract the known absorption of the reagent the resulting subtraction curve should be that of the $R—[CR'=CH]_n—CH=N-$ chromophore (where $n = 0$, 1, 2, 3, etc., and R and R′ may be either H or alkyl groups).

The numerical data are given in Table I, whilst Figs. 1, 2, and 3 show the absorption curves of only a few of the more typical examples. The occurrence of low-intensity absorption bands between 270 and 360mμ in some of the subtraction curves is still unexplained, but this does not appear to affect the main conclusions.

TABLE I.

Spectroscopic Data on 2 : 4-Dinitrophenylsemicarbazones.

Parent carbonyl compound.	$\lambda_{max.}$, A.	ε.	Subtraction curve. $\lambda_{max.}$, A.	Subtraction curve. ε.	No. of ethylene links or equivalent.
Simple aldehydes and ketones.					
Acetaldehyde	2285 2640 3200	19,400 12,600 16,500	2325	8,400	1
Methyl ethyl ketone	2275 2630 3200	20,000 11,800 15,900	2300	8,800	1
Methyl *n*-propyl ketone	2280 2650 3205	19,200 11,000 15,800	2300	8,000	1
*cyclo*Hexanone	2295 2640 3205	19,300 10,800 15,400	2325	8,400	1
αβ-Unsaturated aldehydes and ketones.					
Mesityl oxide	2600 3220	22,600 17,400	2600	12,000	2
3-Methylpent-3-en-2-one	2600 3225	24,000 15,800	2610	13,600	2
1-Methyl*cyclo*hexen-3-one	2635 3235	29,800 19,400	2640	19,400	2
Crotonaldehyde	2625 3220	32,200 19,100	2640	21,800	2
Dienones.					
ψ-Ionone	3075	40,000	3000	27,500	3
Hepta-3 : 5-dien-2-one	2875	37,700	2850	30,100	3
Aromatic compounds.					
Benzaldehyde	2725 3145	23,800 22,300	2790	15,600	2½
Acetophenone	2650 3175	25,000 20,000	2650	14,800	2½
Cinnamaldehyde	3220	45,000	3250	30,200	3½
Benzylideneacetone	3150	39,700	3100	25,300	3½
Citrylidenecrotonaldehyde	3290	41,500	3360	28,200	4
2 : 4-Dinitrophenylsemicarbazide	2610 3220	10,500 14,900	—	—	

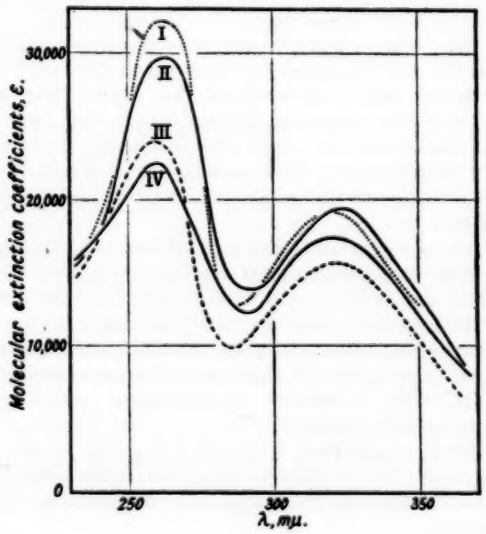


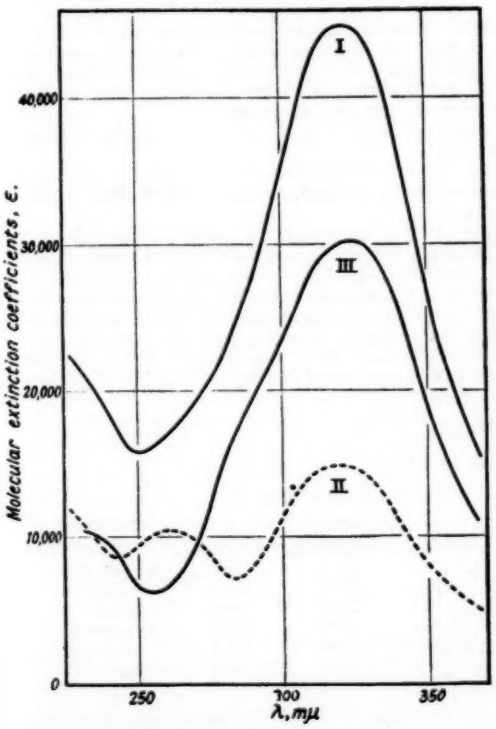
FIG. 2.

Dinitrophenylsemicarbazones (absorption spectra in alcohol):

I. *Crotonaldehyde.*
II. 1-*Methyl*cyclo*hexen*-3-*one.*
III. 3-*Methylpent*-3-*en*-2-*one.*
IV. *Mesityl oxide.*

The subtraction-curve data in Table I show the steady displacement of the maxima to longer wave-lengths as the length of the conjugated system in the non-semicarbazide part of the molecule increases. This is shown more clearly in Fig. 4. The fact that the two types of aromatic carbonyl derivative show displacements which are respectively equivalent to $2\frac{1}{2}$ and $3\frac{1}{2}$ ethylene linkages supports the suggestion of Kuhn, Haüsser, *et al.* (*Z. physikal. Chem.*, 1935, **29**, *B*, 363) that a benzene nucleus in conjugation with one or more ethylene linkages is equivalent to $1\frac{1}{2}$ of such bonds.

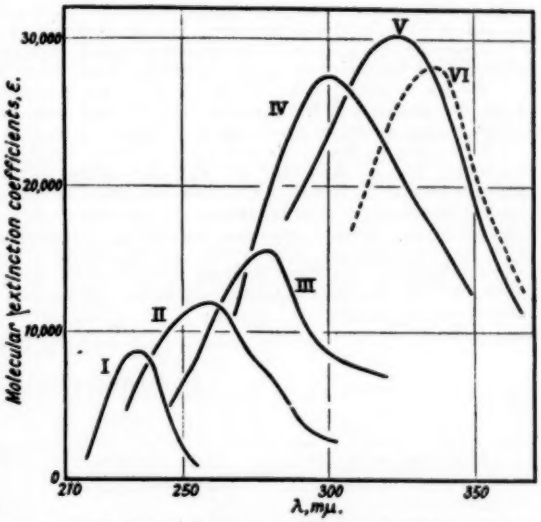
FIG. 3.



Absorption spectra in alcohol :

I. *Cinnamaldehyde* 2 : 4-*dinitrophenylsemicarbazone.*
II. *Reagent.*
III. *Subtraction curve.*

FIG. 4.



2 : 4-*Dinitrophenylsemicarbazone subtraction curves :*

I. *Simple ketone* (cyclo*hexanone*).
II. *αβ-Unsaturated ketone* (*mesityl oxide*).
III. *Simple aromatic aldehyde* (*benzaldehyde*).
IV. *Dienone* (*ψ-ionone*).
V. *Unsaturated aromatic aldehyde* (*cinnamaldehyde*).
VI. *Trienal* (*citrylidenecrotonaldehyde*).

The validity of the generalisation that two unconjugated chromophores in a molecule produce an approximate summation of the effects due to each can be checked within this particular series, since the observed absorption of the 2 : 4-dinitrophenylsemicarbazones when

TABLE II.

Comparison of Direct Absorption Data on Semicarbazones with Subtraction Curves via *the* 2 : 4-*Dinitrophenylsemicarbazones.*

Parent carbonyl compound.	Direct absorption spectrum of semicarbazone.		Subtraction curve *via* 2 : 4-dinitrophenylsemicarbazone.	
	$\lambda_{max.}$, A.	ε.	$\lambda_{max.}$, A.	ε.
*cyclo*Hexanone	2295	11,200	2325	8,400
Mesityl oxide	2600	12,000	2600	12,000
Crotonaldehyde	2645	24,000	2640	21,800
1-Methyl*cyclo*hexen-3-one.	2655	25,700	2640	19,400
ψ-Ionone	2995	45,400	3000	27,500
Hepta-3 : 5-dien-2-one	2900	37,000	2850	30,100
Benzaldehyde	2825	19,900	2790	15,600
Acetophenone	2715	17,780	2650	14,800

corrected for the separate absorption of the reagent itself should yield a subtraction curve comparable with the known and directly observed absorption spectra of the simple semicarbazones. The available data are given in Table II, and, considering the number of variables concerned in obtaining the data, the general agreement is good, being better in terms of location of the band than where intensities are concerned. The values for ψ-ionone are noticeably discrepant in this latter respect.

Experimental.

1-Methyl*cyclo*hexen-3-one was prepared by condensation of formaldehyde and acetoacetic ester followed by ring-closure of the methylenediacetoacetic ester (Knoevenagel, *Annalen*, 1894, **281**, 94); b. p. 200°.

3-Methylpent-3-en-2-one was prepared by condensation of acetaldehyde and methyl ethyl ketone (Hinkel, *J.*, 1931, 817). The ketone was crystallised from benzene to constant m. p., but the N content was low (Found: N, 19·6. Calc.: N, 21·8%). This might have been due to retention of solvent as the spectroscopic data were quite normal. Attempted purification by chromatography gave slight evidence of lack of homogeneity, but no increase in purity was in fact achieved.

ψ-Ionone was prepared by condensation of acetone and citral (Stiehl, *J. pr. Chem.*, 1898, **58**, 79) and crystallised successively from chloroform and chlorobenzene.

We are indebted to Dr. E. R. H. Jones for a sample of citrylidenecrotonaldehyde which was isolated from the products of the condensation of citral with crotonaldehyde (cf. Batty *et al.*, *J.*, 1937, 756; 1939, 1559). The specimen used had $\lambda_{max.}$ 3140 A.; $\varepsilon = 14{,}500$.

2 : 4-*Dinitrophenylsemicarbazones*.—These were prepared by dissolving 2 : 4-dinitrophenylsemicarbazide (0·5 g.) in alcohol (80 ml.) and adding to the boiling solution slightly less than the theoretical amount of the carbonyl compound dissolved in the minimum of alcohol. After addition of concentrated hydrochloric acid (2 drops) the solution was boiled for ten minutes after which the precipitated derivative was filtered off, being usually only very sparingly soluble in alcohol even at the boiling point. For recrystallisation chloroform was found to be the most useful solvent and derivatives were recrystallised to constant melting point, two or three crystallisations being usually sufficient. All the 2 : 4-*dinitrophenylsemicarbazones* in Table III are new except that of methyl ethyl ketone (cf. McVeigh and Rose, *loc. cit.*).

Table III.

2 : 4-*Dinitrophenylsemicarbazones*.

Aldehyde or ketone.	M. p. of deriv.	Formula.	Nitrogen, %. Calc. or required.	Found.	Recrystallised from:
Methyl ethyl ketone	235° (decomp.)	$C_{11}H_{13}O_5N_5$	23·7	23·7	Chloroform
Mesityl oxide	207 ,,	$C_{13}H_{15}O_5N_5$	21·8	21·4	Chloroform
3-Methylpent-3-en-2-one ...	236·5 ,,	$C_{13}H_{15}O_5N_5$	21·8	19·6	Benzene
1-Methyl*cyclo*hexen-3-one	227·5 ,,	$C_{14}H_{15}O_5N_5$	21·0	20·7	Chloroform
ψ-Ionone	227 ,,	$C_{20}H_{25}O_5N_5$	16·9	16·1	Chlorobenzene
Hepta-3 : 5-dien-2-one	240 ,,	$C_{14}H_{15}O_5N_5$	21·0	20·4	Alcohol
Citrylidenecrotonaldehyde	207 (no decomp.)	$C_{21}H_{25}O_5N_5$	16·4	16·1	Alcohol

Absorption spectra were determined by standard methods using a Hilger E3 quartz spectrograph and a Spekker photometer. Purified alcohol was used as solvent throughout, although the very low solubility of the 2 : 4-dinitrophenylsemicarbazones made this difficult at times. The high intensity of absorption in some cases made it possible to use very dilute solutions for the determination, and the concentrations usually ranged between 0·03 and 0·003% only. The solutions were made by dissolving 2—3 mg. of the compound in hot alcohol, cooling, and making up to suitable volume, *e.g.*, 100 ml. All determinations were made in duplicate, the $\lambda_{max.}$ and $\varepsilon_{max.}$ values being taken from the mean curves.

Our thanks are due to Miss McVeigh and Dr. F. L. Rose for specimens of a number of the compounds examined.

The University of Manchester. [*Received, December 19th*, 1946.]

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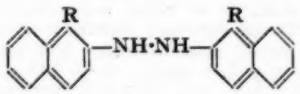
259. *The Naphthidine Transformation involving β-Positions only.*

By Herbert H. Hodgson, John Habeshaw, and P. B. R. Murti.

1 : 1′-*Dichloro*- and 1 : 1′-*dibromo*-2 : 2′-*diamino*-3 : 3′-*dinaphthyl* are most probably formed in the reduction of 1 : 1′-dichloro- and 1 : 1′-*dibromo*-2 : 2′-azonaphthalene by stannous chloride in ethyl alcohol–hydrochloric acid solution. 1-Bromo-2-naphthalenediazoacetate decomposes at ordinary temperatures to give 1-*bromo*-2-*naphthaleneazo*-β-*naphthol*.

The naphthidine transformations already reported have involved α- and αβ-positions only (Nietzki and Goll, *Ber.*, 1885, **18**, 3254; Veselý, *Ber.*, 1905, **38**, 136; Meisenheimer and Witte, *Ber.*, 1903, **36**, 4153; Hodgson and Habeshaw, this vol., p. 77). It is of interest also that,

in the transformation of 1 : 1′-hydrazonaphthalene, the 2- and 4-positions exhibit approximately equal activity (cf. Hodgson and Habeshaw, *loc. cit.*) while no mixed 1 : 1′-diamino-2 : 4′-dinaphthyl has ever been detected among the transformation products. No change involving the 2 : 3- (*i.e.*, solely β-positions) transformation has hitherto been reported, and, in view of the fact that among the possible resonance structures of a 1 : 1′-substituted -2 : 2′-hydrazonaphthalene there is one (I) which indicates that such a change might be possible, it appeared of interest



(I.)

to investigate whether this 2 : 3-naphthidine change would occur in the cases of 1 : 1′-dichloro- and 1 : 1′-dibromo-2 : 2′-hydrazonaphthalenes (I; R = Cl or Br) since such compounds might be formed intermediately by the action of stannous chloride in ethyl alcohol–hydrochloric acid suspensions of 1 : 1′-dichloro- and 1 : 1′-*dibromo*-2 : 2′-azonaphthalenes (cf. Cohen and Oesper, *Ind. Eng. Chem. Anal.*, 1936, **8**, 306).

As anticipated, dinaphthyl formation occurred and in all probability 1 : 1′-*dichloro*- and 1 : 1′-*dibromo*-2 : 2′-*diamino*-3 : 3′-*dinaphthyls* were formed, so that the naphthidine transformation had taken place between β-positions only. When the reduction of the above halogeno-azo-compounds was carried out with stannous chloride and hydrochloric acid in the absence of ethyl alcohol, cleavage occurred between the nitrogen atoms of the azo-group, and 1-chloro- and 1-bromo-2-naphthylamine were formed respectively. The constitutions of the above dinaphthyls were tentatively established by the fact of dihydrochloride formation in the cases of the chloro- and bromo-compounds, and of the tetrazotisation of the 1 : 1′-dibromo-2 : 2′-diamino-3 : 3′-dinaphthyl and subsequent coupling with alkaline β-naphthol to give a bisazo-compound. Since halogens were not displaced, it is most unlikely that dinaphthyl formation would involve the 4 : 4′-positions.

When a solution of 1-bromo-2-naphthalenediazoacetate was allowed to decompose at ordinary temperatures, 1-*bromo*-2-*naphthaleneazo*-β-*naphthol* was produced, an indication that 1-bromo-2-naphthol must first have been formed, by hydrolysis of the diazoacetate, and that unchanged diazo-compound subsequently coupled with it in the 1-position by displacement of the 1-bromine atom.

Experimental.

1 : 1′-*Dichloro*-2 : 2′-*diamino*-3 : 3′-*dinaphthyl*.—1 : 1′-Dichloro-2 : 2′-azonaphthalene (5 g.) (compare Hodgson, Leigh, and Turner, *J.*, 1942, 744) was boiled gently with ethyl alcohol (50 c.c.) and a solution of crystallised stannous chloride (10 g.) in hydrochloric acid (25 c.c., *d* 1·18) added gradually with shaking. During this addition, all the solid passed into solution, and, after the mixture had been kept on the boiling water-bath for 10 minutes, it was cooled and then treated with hydrochloric acid (25 c.c., *d* 1·18); 1 : 1′-*dichloro*-2 : 2′-*diamino*-3 : 3′-*dinaphthyl dihydrochloride* then separated (1·6 g.) in colourless crystals which were filtered off and washed with ether; it was soluble in water, evolved hydrogen chloride on treatment with concentrated sulphuric acid with formation of a yellow solution, and decomposed on heating at *ca.* 400° (Found : Cl, 33·2. $C_{20}H_{16}N_2Cl_4$ requires Cl, 33·3%).

1 : 1′-*Dichloro*-2 : 2′-*diamino*-3 : 3′-*dinaphthhthyl* was obtained as a white flocculent precipitate, which coagulated somewhat on standing and became biscuit coloured, when warm aqueous sodium carbonate was stirred into a warm aqueous solution of the above dihydrochloride; it was filtered off, washed, dried, and crystallised from benzene–light petroleum (1 : 1) in small colourless needles, m. p. 121—122° (Found : N, 8·1; Cl, 19·8. $C_{20}H_{14}N_2Cl_2$ requires N, 7·9; Cl, 20·1%), which soon became discoloured in air and were moderately soluble in ethyl alcohol; the alcoholic solution, however, rapidly oxidised and became reddish-violet, a red film forming on the wall of the glass container.

Preparation of 1-*Bromo*-2-*naphthylamine*.—A solution of β-naphthylamine (28 g.) in glacial acetic acid (200 c.c.) containing acetic anhydride (25 c.c.) was heated on the boiling water-bath for 20 minutes to complete the acetylation, and then treated dropwise with the theoretical amount of bromine (32 g.) during continuous stirring. The resulting 1-bromoaceto-2-naphthalide was precipitated by dilution with water in quantitative yield, the precipitate dissolved in alcohol (250 c.c.), hydrochloric acid (30 c.c., *d* 1·18) added, and the mixture boiled for 6 hours to complete the hydrolysis; 1-bromo-2-naphthylamine was then precipitated by addition of 20% aqueous sodium hydroxide, purified by crystallisation from light petroleum, and obtained in colourless needles, m. p. 63° (Cosiner, *Ber.*, 1881, **14**, 59, gives m. p. 63°) (Found : Br, 35·8. Calc. for $C_{10}H_8NBr$: Br, 36·0%).

1-*Bromo*-2-*naphthaleneazo*-β-*naphthol*, obtained by diazotisation of the above amine and coupling with alkaline β-naphthol in the usual way, crystallised from toluene in dark red parallelepipeds, m. p. 169—170° (Found : N, 7·5; Br, 21·0. $C_{20}H_{13}ON_2Br$ requires N, 7·4; Br, 21·2%), which gave with concentrated sulphuric acid a bright red-violet colour turning to crimson on dilution with water.

1-*Bromo*-2-*naphthaleneazo*-β-*naphthylamine*, obtained by diazotisation of the above amine in aqueous hydrochloric acid and coupling with an alcoholic solution of β-naphthylamine in the presence of acetic acid and sodium acetate (cf. Hodgson and Foster, *J.*, 1941, 755), crystallised from toluene in scarlet plates, m. p. 174—175° (Found : N, 11·3; Br, 20·8. $C_{20}H_{14}N_2Br$ requires N, 11·2; Br, 21·0%), which

gave with concentrated sulphuric acid a blue colour turning to red and then to orange-yellow on addition of water.

1 : 1′-*Dibromo*-2 : 2′-*azonaphthalene*.—A mixture of finely divided 1-bromo-2-naphthylamine (5 g.) in hydrochloric acid (25 c.c., *d* 1·18) and water (50 c.c.) was diazotised by addition of a solution of sodium nitrite (2 g.) in water (10 c.c.) with stirring at 0°, the resulting yellow solution filtered, treated rapidly under vigorous stirring with crystallised sodium acetate (40 g.) dissolved in the minimum amount of water to remove mineral acid, and then immediately followed by a solution of crystallised sodium sulphite (10 g.) in water (50 c.c.). A light brown precipitate immediately separated (5·7 g.), and after the mixture had been stirred for 30 minutes at room temperature, when no further reaction of the precipitate with alkaline β-naphthol was detected (absence of diazo-sulphite, cf. Hodgson and Marsden, *J.*, 1943, 470), it was heated to 60° and filtered. The precipitate of 1 : 1′-*dibromo*-2 : 2′-*azonaphthalene* crystallised from benzene in yellow plates, m. p. 193—195° (Found: N, 6·6; Br, 36·2. $C_{20}H_{12}N_2Br_2$ requires N, 6·4; Br, 36·4%), which gave with concentrated sulphuric acid a Bordeaux-red solution turning to scarlet on addition of water.

When the solution of 1-bromonaphthalenediazonium chloride above was treated with sodium acetate only, 1-bromo-2-naphthaleneazo-β-naphthol separated on keeping; it crystallised from toluene in red parallelepipeds, m. p. and mixed m. p. with authentic specimen 168—170° (Found: N, 7·5; Br, 21·0%). If an inadequate amount of sodium acetate is added before the sodium sulphite, the resulting 1 : 1′-dibromo-2 : 2′-azonaphthalene is mixed with the azo-β-naphthol dye above.

1 : 1′-*Dibromo*-2 : 2′-*diamino*-3 : 3′-*dinaphthyl*.—A suspension of 1 : 1′-dibromo-2 : 2′-azonaphthalene (5 g.) in ethyl alcohol (50 c.c.) was heated on the boiling water-bath during the gradual addition with vigorous shaking of a solution of crystallised stannous chloride (10 g.) in hydrochloric acid (25 c.c., *d* 1·18), and the boiling continued (30 minutes) until most of the suspended matter had passed into a nearly colourless solution. The mixture was filtered hot, cooled, hydrochloric acid (20 c.c., *d* 1·18) added, the precipitate (*a*) filtered off, and the solution kept; crystals (*b*) of 1 : 1′-*dibromo*-2 : 2′-*diamino*-3 : 3′-*dinaphthyl dihydrochloride* then separated. Crystals (*b*) were filtered off and washed with ether (Found: Ionic Cl, 13·6. $C_{20}H_{14}N_2Br_2,2HCl$ requires Cl, 13·8%). Precipitate (*a*) and crystals (*b*) were repeatedly stirred with hydrochloric acid (5 c.c., *d* 1·18) and water (10 c.c.), aqueous sodium nitrite was added until a positive reaction for free nitrous acid was obtained, the mixtures were filtered, and the resulting solutions of 1 : 1′-dibromo-3 : 3′-dinaphthyl-2 : 2′-tetrazonium chlorides were stirred into alkaline β-naphthol; in each case 1 : 1′-*dibromo*-3 : 3′-*dinaphthyl*-2 : 2′-*bisazo*-β-*naphthol* separated; this compound crystallised from toluene in red micro-plates, m. p. 315° (Found: N, 7·6; Br, 21·1. $C_{40}H_{24}O_2N_4Br_2$ requires N, 7·4; Br, 21·3%), which give a brilliant blue-violet colour with concentrated sulphuric acid.

The dihydrochloride [crystals (*b*) above] was cautiously decomposed with sodium carbonate or ammonia at about 60°; the resulting *base* crystallised from toluene–light petroleum in minute colourless needles, m. p. 117° (Found: N, 6·5; Br, 36·0. $C_{24}H_{14}N_2Br_2$ requires N, 6·3; Br, 36·2%).

The authors are indebted to Imperial Chemical Industries Ltd., Dyestuffs Division, for various gifts.

TECHNICAL COLLEGE, HUDDERSFIELD. [*Received, December 19th*, 1946.]

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260. *The Replacement of the Diazonium by the Nitro-group. Part III. Decompositions by Cupro-cupri Sulphite.*

By HERBERT H. HODGSON, A. P. MAHADEVAN, and EDWARD R. WARD.

Solid aryldiazonium sulphates are first prepared and their aqueous solutions decomposed by cupro-cupri sulphite suspended in saturated aqueous sodium nitrite, yields up to 65% of nitro-compound being obtained. The precipitate obtained by addition of aqueous sodium sulphite to aqueous copper sulphate appears to be more efficient than the red-violet variety hitherto used. The method is useful for the preparation of rare dinitronaphthalenes of which six examples are given.

THE solid diazonium sulphates obtained by the general method of Hodgson and Mahadevan (this vol., p. 325) are readily decomposed when added either in aqueous solution or in solid form to a saturated solution of sodium nitrite containing cupro-cupri sulphite in suspension (cf. Hantzsch and Blagden, *Ber.*, 1900, **33**, 2544; Contardi, *Annali Chim. Appl.*, 1923, **7**, 13) to give excellent yields of the corresponding nitro-compounds. In particular, the method has proved to be exceedingly serviceable for obtaining the rarer dinitronaphthalenes in excellent yield and purity, and has also worked satisfactorily with benzidine, 3 : 3′-dinitrobenzidine, and 3 : 5-dinitro-*p*-toluidine. The cupro-cupri sulphite used was prepared by the addition of aqueous sodium sulphite to an equivalent amount of aqueous copper sulphate, and the greenish yellow-brown gelatinous precipitate, when washed free from excess of either component, was stirred as a slurry into the saturated aqueous sodium nitrite. So prepared, this variety of cupro-cupri sulphite appeared to be more efficient than the red-violet crystalline precipitate obtained by the addition of aqueous ammonium sulphite saturated with sulphur dioxide to warm aqueous copper sulphate and raising the temperature to 90° for 10 minutes (Mellor, " A Comprehensive Treatise on Inorganic and Theoretical Chemistry ", Vol. X, pp. 273—277).

The preparation of some solid diazonium sulphates (*e.g.*, that from 3-nitro-*p*-toluidine) involves the use of minimum amounts of acetic and sulphuric acids, and for this purpose the inverted diazotisation procedure of Hodgson and Walker (cf. Hodgson and Turner, *J.*, 1943, 86) has been used, *viz.*, a solution of the amine in the minimum amount of concentrated sulphuric acid is treated with solid sodium nitrite and the mixture stirred into glacial acetic acid; with 3-nitro- and 3 : 5-dinitro-*p*-toluidine, the temperature could safely be allowed to reach 40° during the addition of the sodium nitrite without loss of yield of the resulting diazonium salt.

Usually, the solid diazonium sulphate, after precipitation by ether from the diazotisation medium, is dissolved in water at 0° before the cupro-cupri sulphite treatment, but it is essential first to remove admixed acid from it by washing with alcohol or ether or both. When these precautions are observed, 2-nitro-1- and 1-nitro-2-naphthylamine, which require the glacial acetic–sulphuric acid method (Hodgson and Walker, *J.*, 1933, 1620) for their diazotisation, afford the respective diazonium sulphates, the former of which readily dissolves in cold water; both form solutions which remain stable for periods of time amply sufficient for the subsequent manipulation. If, instead of first isolating the solid diazonium sulphates, the solutions of these diazonium salts as prepared by the Hodgson and Walker method (*loc. cit.*) are diluted with water and then neutralised before the cupro-cupri sulphite treatment, diazo-oxide formation occurs rapidly and no dinitronaphthalene can be obtained (cf. Veselý and Dvorák, *Bull. Soc. chim.*, 1923, **33**, 319, who failed to obtain 1 : 2-dinitronaphthalene from 1-nitro-2-naphthylamine from this cause).

The co-precipitation of sodium sulphate in almost anhydrous form with the solid diazonium sulphate probably accounts for the separation of the latter in a satisfactory crystalline state free from the stickiness usually encountered in the ordinary mode of diazonium salt isolation, since any water present will be bound by the sodium sulphate.

Addition of solid diazonium sulphate to the decomposition medium is not usually satisfactory, owing to formation of tar, probably because of local overheating during decomposition, while the tendency for hydroxylic by-products (phenols or naphthols as indicated by dissolution in alkalis), or small amounts of azo-compounds (as indicated by colour reactions) is enhanced.

It has been found that aryldiazonium cobaltinitrities (cf. Hodgson and Marsden, *J.*, 1944, 22) can be satisfactorily decomposed by adding them in aqueous suspension to the aqueous cupro-cupri sulphite–sodium nitrite mixture. Incidentally, steric hindrance appears to retard the formation of diazonium cobaltinitrites, for whereas tetrazotised 4 : 4′-dichloro-3 : 3′-diaminodiphenyl eventually affords an 85—90% yield of its tetrazonium cobaltinitrite, the formation is slow compared with that of tetrazotised benzidine.

It is of interest that the colours of 2-nitronaphthalene-1-diazonium sulphate and of 1-nitro-2-diazonium sulphate are yellow-orange and red-orange like those of the parent 2-nitro-1- and 1-nitro-2-naphthylamines.

Contardi and Mor (*Rend. Ist. Lomb. Sci. Lett.*, 1924, **57**, 646; *Annali Chim. Appl.*, *loc. cit.*), from a study of the replacement of the diazonium by the nitro-group for more than 40 different amines, conclude that the introduction of the nitro-group is facilitated when nitro-groups or halogens are present in the nucleus of the amine, and this is in accord with the viewpoint of Hodgson, Leigh, and Turner (*J.*, 1942, 744) who postulated the ease of replacement of the diazonium group to depend on the positivity of the carbon atom to which the diazonium group is attached, *viz.*, the greater the positivity, the readier the replacement by halogens or the nitro-group, and the less the positivity, the greater the proneness to attack by anionoid water with replacement of the diazonium by the hydroxyl group and formation of phenols or naphthols. The reactivity of cupri-salts for replacement of diazonium by nitro-groups as found by Contardi *et al.*, and also by Hodgson and Marsden (*loc. cit.*) for the decomposition of aryldiazonium cobaltinitrites, is evidence which supports the interpretation of the Sandmeyer reaction given by Hodgson, Birtwell, and Walker (*J.*, 1941, 770; 1942, 720).

Experimental.

General Decomposition Procedure as indicated by the Preparation of 1 : 4-*Dinitronaphthalene.*—Powdered sodium nitrite (10 g.) was stirred into sulphuric acid (50 c.c., *d* 1·84), and the mixture treated gradually below 20° (external cooling) with a solution of 4-nitro-1-naphthylamine (10 g.) in glacial acetic acid (100 c.c.), and subsequently stirred for 20 minutes. Ether (700 c.c.) was next stirred into the solution at 0°, the mixture kept for 1 hour, the crystalline precipitate (by scratching) of 4-nitronaphthalene-1-diazonium sulphate filtered off, washed free from acid with ether, and dissolved in water (100 c.c.), and the solution stirred slowly into the mixture of cupro-cupri sulphite prepared as follows. An aqueous solution of crystallised sodium sulphite (50 g.) was stirred into one of crystallised copper sulphate (50 g.), and the greenish yellow-brown precipitate filtered off, washed with water, ground into a slurry with water, and then stirred into a mixture of sodium nitrite (100 g.) in water (400

c.c.). Decomposition was very rapid (cf. Hantzsch and Blagden, *loc. cit.*), and foam was broken periodically by addition of small amounts of ether; after 1 hour's stirring, when most of the inorganic matter has passed into the dark green solution, the precipitate of crude 1 : 4-dinitronaphthalene was filtered off, washed in the sequence, water, dilute sodium hydroxide, and water, dried, and crystallised from aqueous methyl alcohol from which it separated in pale yellow needles, m. p. 133·5° (Hodgson and Hathway, *J.*, 1945, 453, give m. p. 134°) (Found: N, 13·0. Calc. for $C_{10}H_6O_4N_2$: N, 12·8%); or, it can be purified by steam distillation, which for this compound is a rather slow process. Yield of pure 1 : 4-dinitronaphthalene, 7·5 g. (*ca.* 65%). Usually, where a readily volatile nitro-compound is formed, the steam method of removal is the more convenient.

Estimation of Yield of Diazonium Sulphate.—The solution of the diazonium sulphate in water was made up to a definite volume, an aliquot portion stirred into the alkaline β-naphthol, the precipitated arylazo-β-naphthol removed, washed, dried, and weighed, and the corresponding amount of aryl- or naphthyl-diazonium sulphate calculated.

Preparation of 3 : 3′ : 4 : 4′-Tetranitrodiphenyl.—3 : 3′-Dinitrobenzidine (5 g.) was dissolved in sulphuric acid (25 c.c., *d* 1·84), powdered sodium nitrite (5 g.) added gradually below 40°, and the mixture stirred below 20° into glacial acetic acid (50 c.c.); after 30 minutes, ether (200 c.c.) was added at 0°, the mixture kept for 1 hour, and the precipitated solid tetrazonium sulphate filtered off and dealt with as by the general method. The crude 3 : 3′ : 4 : 4′-tetranitrodiphenyl was filtered off, washed with water, dilute sodium hydroxide, and finally with water, dried, extracted with boiling toluene (250 c.c.), and the extract concentrated to 25 c.c.; 3 : 3′ : 4 : 4′-tetranitrodiphenyl crystallised out, m. p. 188—190°, and separated subsequently from boiling 80% acetic acid in clusters of yellow needles, m. p. 191—193° (Ullmann and Bielecki, *Ber.*, 1901, **34**, 2129, give m. p. 186°) (Found: N, 16·9. Calc. for $C_{12}H_6O_8N_4$: N, 16·8%).

Preparation of 3 : 4 : 5-Trinitrotoluene.—Solid sodium nitrite (5 g.) was stirred into sulphuric acid (25 c.c., *d* 1·84), and 3 : 5-dinitro-*p*-toluidine (5 g.) was stirred below 40° into this mixture, which was then added gradually below 20° to glacial acetic acid (50 c.c.). After 30 minutes, ether (200 c.c.) was added at 0°, and the precipitated diazonium sulphate dealt with as above. After decomposition, the crude 3 : 4 : 5-trinitrotoluene was extracted thrice with boiling toluene (150 c.c. in all), and the extract concentrated to 15 c.c.; magnificent monoclinic needles of an almost pure product separated (1·3 g., m. p. 135°) (Körner and Contardi, *Atti R. Accad. Lincei*, 1915, [5], **24**, 892, give m. p. 137·5°) (Found: N, 18·7. Calc. for $C_7H_5O_6N_3$: N, 18·5%).

Amine taken.	Nitro-compound formed.	Yield of pure compound (%). (*a*) With slurry.	(*b*) With red-violet solid.	Remarks.
β-Naphthylamine	β-Nitronaphthalene	40	30	Calc. on amine taken
,,	,,	57	40	Calc. on diazonium sulphate isolated
2-Nitro-1-naphthylamine	1 : 2-Dinitronaphthalene	53	—	Calc. on diazonium sulphate isolated
1-Nitro-2-naphthylamine	1 : 2-Dinitronaphthalene	15	—	Calc. on diazonium sulphate isolated
4-Nitro-1-naphthylamine	1 : 4-Dinitronaphthalene	65	—	Calc. on amine taken
5-Nitro-2-naphthylamine	1 : 6-Dinitronaphthalene	55	—	,, ,,
8-Nitro-2-naphthylamine	1 : 7-Dinitronaphthalene	45	30—40	,, ,,
6-Nitro-2-naphthylamine	2 : 6-Dinitronaphthalene	45	—	,, ,,
Benzidine	4 : 4′-Dinitrodiphenyl	16	—	,, ,,
3 : 3′-Dinitrobenzidine	3 : 3′ : 4 : 4′-Tetranitrodiphenyl	55	—	,, ,,
3 : 5-Dinitro-*p*-toluidine	3 : 4 : 5-Trinitrotoluene	25	—	,, ,,

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261. *The Reaction between Acetone and Ammonia: The Formation of Pyrimidine Compounds Analogous to the Aldoxans of Späth.*

By R. B. BRADBURY, N. C. HANCOX, and H. H. HATT.

The reaction of acetone with ammonia can be conducted to give 90% yields of the monohydrate of 2 : 2 : 4 : 4 : 6-pentamethyl-2 : 3 : 4 : 5-tetrahydropyrimidine, which is readily dehydrated to the anhydrous base. By reduction with sodium in alcohol it gives the corresponding hexahydropyrimidine, and with aluminium amalgam an open chain primary-secondary diamine, $C_9H_{22}N_2$. The hexahydropyrimidine is hydrolysed with extreme ease to 2 : 4-diamino-2-methylpentane and acetone.

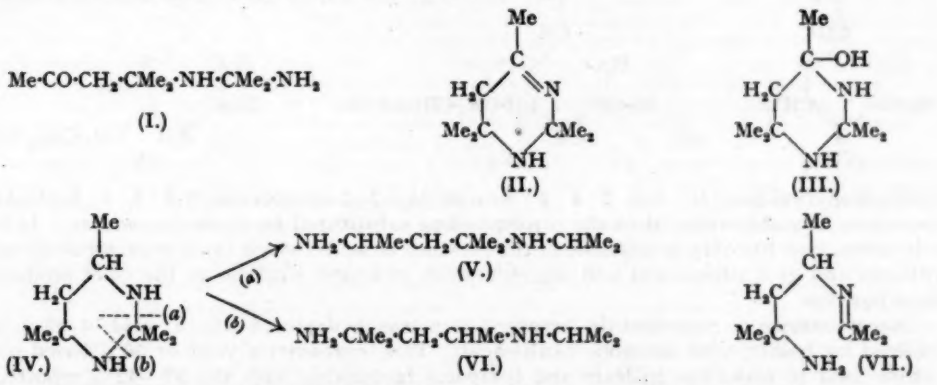
The mechanism of the formation of (II) is discussed in the light of its synthesis from mesityl oxide, acetone, and ammonia, and its quantitative hydrolysis to diacetonamine.

Mesityl oxide and ammonia can be condensed to produce a substituted tetrahydropyrimidine analogous in structure to paraldol.

DIACETONAMINE and triacetonamine can both be obtained from the reaction of acetone with ammonia followed by acidification of the reaction products, and Heintz (*Annalen*, 1874, **174**, 133) first showed that triacetonamine was produced if the reaction mixture was heated, but that at room temperature diacetonamine was the chief product. The preparation of these compounds has since been improved by the use of calcium chloride to hasten the absorption of ammonia and to assist in the removal of water (Everest, *J.*, 1919, **115**, 588; Francis, *J.*, 1927, 2897). Further Suzuki and Horie (*Bull. Inst. Phys. Chem. Res. Japan*, 1932, **11**, 383) have found that the formation of diacetonamine was catalysed by ammonium salts, especially the nitrate and nitrite. Other compounds have been obtained from this reaction. Hock and Stuhlmann (*Ber.*, 1928, **61**, 470) by working at low temperatures isolated a compound C_3H_9ON which, as it decomposed at room temperatures into acetone and ammonia, they regarded as the initial product of the reaction analogous to aldehyde-ammonia. Patterson and McMillan (*J.*, 1921, **119**, 267) found that after a protracted reaction period a compound $C_9H_{20}ON_2$ could be obtained by cooling, to which they assigned structure (I). It has not hitherto been further investigated.

We have now found that, by the use of ammonium chloride and calcium chloride as catalysts, this compound is formed in 90% yield from acetone in 24 hours. From examination of its properties we conclude that it is a *hydrate* of **2 : 2 : 4 : 4 : 6-*pentamethyl*-2 : 3 : 4 : 5-*tetrahydropyrimidine*** (II) to which it can be readily dehydrated over sodium hydroxide or sulphuric acid, or by distillation alone or with benzene as entrainer. The anhydrous base readily absorbs water to re-form the hydrate, and the facility of these changes is evidence for the hydrate structure assigned rather than the possible alternative (III). It seems possible that (II) may be identical with the compound $C_9H_{18}N_2$ named " acetonin " by Städeler (*Annalen*, 1859, **111**, 305; Mulder, *ibid.*, 1873, **168**, 229).

The base (II) is readily hydrolysed by boiling water to mesityl oxide, acetone, and ammonia, and by oxalic acid to ammonium and diacetonamine hydrogen oxalates and acetone. The observed molecular refraction (47·8) of the anhydrous base agrees well with the value calculated for structure (II) (47·84). Further support to this structure is given by the observation that both (II) and its hydrate are reduced by sodium and alcohol to **2 : 2 : 4 : 4 : 6-*pentamethylhexahydropyrimidine*** (IV) and that a ***diamine*** of structure (V) or (VI) is produced by the action of aluminium amalgam on (II), its hydrate, or (IV).



The pentamethylhexahydropyrimidine (IV) is hydrolysed more readily than the parent hexahydropyrimidine, first described by Titherley and Branch (*J.*, 1913, **103**, 330), yielding 2 : 4-diamino-2-methylpentane and acetone rapidly with dilute acids and slowly with water alone. Although it is readily converted into open chain compounds, there is no evidence for the co-existence of the Schiff's base (VII), for, unlike hexahydropyrimidine, (IV) distils without the formation of a resinous polymer and the observed molecular refraction (48·7) agrees closely with that calculated for (IV) (48·77).

Ease of ring fission in the methyl-substituted hydropyrimidines doubtless accounts in part for failure to prepare acyl derivatives, which the presence of imino- and hydroxyl groups in (II), (III), and (IV) suggests as possible. Titherley and Branch (*loc. cit.*) obtained the dibenzoyl derivative of hexahydropyrimidine by normal Schotten–Baumann procedure, but from (II) and its hydrate we obtained only *N*-benzoyldiacetonamine and from (IV) only **2 : 4-*dibenzamido*-2-**

methylpentane. 4 : 4 : 6-*Trimethylhexahydropyrimidine* has been synthesised and shows intermediate properties, giving a little of its *dibenzoyl* derivative together with much 2 : 4-dibenzamido-2-methylpentane. Failure to acylate can be viewed as evidence for the hydrate structure rather than (III), for the imino-group in (II) is sterically almost identically placed with the imino-group of triacetonamine, which forms a hydrate and a nitroso-derivative, but so far has not been benzoylated. Actually (II) reacts with nitrous acid and gives a compound of the expected composition, $C_9H_{17}ON_3$, but the yield is small and the properties are abnormal.

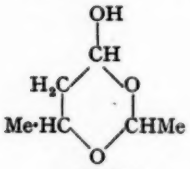
The hydrate of (II) can by synthesised from mesityl oxide, acetone, and ammonia, thus reversing the hydrolysis with acids and suggesting that formation from acetone proceeds by way of diacetonamine and not through the hypothetical intermediate, $CMe_2(NH_2)\cdot CMe_2\cdot OH$, proposed by Patterson and McMillan. The preparation of diacetonamine from acetone and ammonia by the method of Everest therefore involves the formation of the hydrate, followed by its hydrolysis with oxalic acid, the scheme being :

$$\text{Acetone} + \text{Ammonia} \longrightarrow \text{Diacetonamine} \xrightarrow[\text{Acetone and ammonia}]{} \text{Hydrate of (II)} \xrightarrow[\text{Oxalic acid}]{} \text{Diacetonamine.}$$

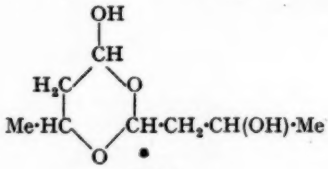
Presumably (II) is also an intermediate in the formation of triacetonamine.

The strong catalytic action of ammonium salts in the formation of (II) can be attributed to their acidic character in a mixture of acetone and ammonia. In support of this view, trimethylammonium chloride, which can still donate a proton, exhibits a like powerful catalytic action, whereas tetramethylammonium chloride, being unable to react in this way, has an action even weaker than calcium chloride. These catalytic effects must apply mainly to the initial formation of diacetonamine, for the hydrate of (II) is formed readily from diacetonamine, acetone, and ammonia in absence of a catalyst.

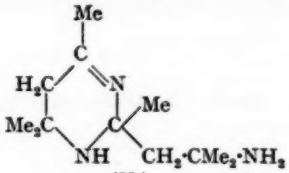
An analogy is apparent between the suggested mechanism for the reaction between acetone and ammonia and that given by Späth for the formation of aldoxan (VIII) by condensation of acetaldehyde (*Ber.*, **1943**, **76**, 57). The reaction between mesityl oxide and ammonia provides a further analogy. When the ammonia used is in excess of that needed to form diacetonamine, a compound of the formula $C_{12}H_{25}N_3$ forms slowly. To this is assigned structure (X), closely analogous to the structure (IX) determined by Späth for paraldol. Like the substituted



(VIII.)



(IX.)



(X.)

tetrahydropyrimidine (II), this 2 : 4 : 4 : 6-*tetramethyl*-2-(2-*amino*isobutyl)-2 : 3 : 4 : 5-*tetrahydropyrimidine* is readily reduced to the corresponding substituted *hexahydropyrimidine*. It forms no hydrate, but, like (II), is unstable in the presence of acids, which cause reversal of the above synthesis and give ammonium and diacetonamine hydrogen oxalates as the chief products of decomposition.

Diacetonamine is conveniently prepared from the hydrate of (II), a yield of 93% being obtained by boiling with alcoholic oxalic acid. This represents a yield of 56% based on the acetone used to make the hydrate and compares favourably with the 37—42% reported by Everest (*loc. cit.*), in which allowance was made for recovered acetone, and with the 70—75% yields from mesityl oxide (*Org. Synth.*, VI, 28; Smith and Adkins, *J. Amer. Chem. Soc.*, **1938**, **60**, 407). The synthesis of 2 : 4-diamino-2-methylpentane from acetone through the hydrate of (II) and (IV) comprises three steps all with yields exceeding 80%, and is preferable to the preparation from acetone proceeding through mesityl oxide, diacetonamine, and its oxime.

Experimental.

(All melting points are corrected.)

2 : 2 : 4 : 4 : 6-*Pentamethyl*-2 : 3 : 4 : 5-*tetrahydropyrimidine Hydrate*.—(*a*) Acetone (290 g., 5 mol.), calcium chloride (" A.R. dried ", 40 g.), and ammonium chloride (10 g.) were cooled in an autoclave to − 40°, and liquid ammonia (110 g., 6·5 mol.) was added. After 24 hours' stirring at room temperature, the solid product was melted by gentle warming (40°), and the top layer separated, allowed to solidify,

and dried on porous plates (yield, 252 g.; 88%). This material is almost pure, but the small amounts of ammonium and calcium chlorides present can be removed by crystallisation from ether.

The amounts of ammonia, ammonium chloride, and calcium chloride stated above are the least for a good yield, and the use of larger amounts does not perceptibly affect the yield. When the reaction time is prolonged to 3 days the yield is increased by 1—2%.

With acetone and ammonia alone the reaction mixture remains liquid for months, although some hydrate is formed and crystallises out on cooling to − 40°. Thus after 7 days a 17% yield is obtained. In presence of ammonium chloride the hydrate forms rapidly, but the solid reaction product does not separate into two layers when melted, and removal of ammonium chloride requires extraction with ether. With calcium chloride alone the yield is smaller even with a longer reaction period. The product, however, forms two liquids; the lower, containing the calcium chloride and water, is easily removed, and the upper when cooled to − 40°, deposits the hydrate. The presence of small amounts of lime in the calcium chloride does not affect the yield. The presence of water is beneficial; thus fused calcium chloride alone and with half its weight of water gave yields of 55 and 65% respectively.

The table summarises the results of experiments in which 290 g. (5 mols.) of acetone and 110 g. (6·5 mols.) of ammonia were used. The reaction took place at room temperatures and the amount of catalyst used was always equivalent to 10 g. of ammonium chloride.

Catalyst.	Calcium chloride (g.).	Time (days).	Yield of (II) (%).	Catalyst.	Calcium chloride (g.).	Time (days).	Yield of (II) (%).
None.....	None	7	17	$NHMe_3Cl$	40	1	85
,, ...	40	4	65–70	NMe_4Cl	40	1	35
NH_4Cl	none	4	70	NMe_4Br	40	4	66
,, ...	40	1	88	$NHMe_3Cl$	none	4	63
NH_4NO_3	40	1	85	NMe_4Cl *	,,	4	35
NH_4Br	40	1	85				

* Added as a 55% aqueous solution.

(*b*) Mesityl oxide (120 g., 1·2 mol.) and ammonia (26 g., 1·5 mol.) were placed in an autoclave cooled to − 40° and stirred for 3 days at room temperature. The mixture was again cooled, acetone (71 g., 1·2 mol.) and ammonia (40 g., 2·4 mol.) were added and the stirring was continued for 4 days. The solid hydrate of (II) was purified by crystallisation from ether (yield, 139 g.; 66%).

The *hydrate* when freshly crystallised from ether forms colourless crystals, m. p. 43—44° [Found: C, 62·4; H, 11·5; N, 16·3; H_2O (by Dean–Stark), 10·5; equiv. (titration), 87. $C_9H_{18}N_2,H_2O$ requires C, 62·7; H, 11·7; N, 16·3; H_2O, 10·5%; equiv., 86]. In air it slowly becomes yellow and decomposes, liberating ammonia, but it can be kept for a considerable time in a stoppered vessel in a refrigerator. It is extremely volatile and sublimes to give large, well-formed crystals of hexagonal habit. It is soluble in cold water (70 g. per 100 ml.), in cold ether (19 g. per 100 ml.), and in most organic solvents.

The *oxalate* was prepared from equimolecular quantities of the hydrate (II) and anhydrous oxalic acid in ether (Found: C, 44·5; H, 7·1; N, 8·0. $C_9H_{20}ON_2,2H_2C_2O_4$ requires C, 44·3; H, 6·8; N, 8·0%).

When to the hydrate (II) and an equivalent amount of aqueous sodium nitrite at 0°, two equivalents of 2N-hydrochloric acid were added, reaction occurred with deposition of a colourless crystalline *substance* during 3 hours (yield, 10—15%), m. p., 168—170° (decomp.) (from acetone). The low yield, high m. p., and decomposition with dilute mineral acid without liberation of nitrous acid conflict with the supposition that it is the nitroso-derivative of (II), although the analytical data are in agreement. Molecular weight determinations gave double the expected values [Found: C, 59·2; H, 8·8; N, 22·8; *M* (in nitrobenzene), 371. $C_9H_{17}ON_3$ requires C, 59·0; H, 9·3; N, 23·0%; *M*, 183).

Diacetonamine Hydrogen Oxalate.—The crude hydrate of (II) (269 g.) prepared from acetone (290 g.) was dissolved in alcohol (300 ml.). An aliquot (5 ml.) was titrated with oxalic acid to determine the amount required (twice that needed for neutralisation: 365 g.). In the titration it is necessary to add about 3/4ths of the estimated amount of acid and then to warm to 80° for a few minutes to complete the hydrolysis of the hydrate. Titration at room temperature as directed by Everest gives low results and leads to the use of insufficient oxalic acid. The oxalic acid was dissolved in alcohol (2000 ml.), stirred vigorously, and the solution of the hydrate added in ½ hour at 30° or less. After a further ½ hour, 100 ml. of the solvent were removed and the ammonium hydrogen oxalate was filtered from the hot solution and extracted thrice with 300 ml. portions of boiling alcohol. The combined filtrates were cooled rapidly, and after 3 hours the diacetonamine hydrogen oxalate was collected and dried (m. p. 123—125°). The mother liquors, on evaporation, yielded a further 20 g. Yield, 309 g.; 56% based on the acetone taken. The maximum yield on this basis is 66·7%.

2 : 2 : 4 : 4 ; 6-*Pentamethyl*-2 : 3 : 4 : 5-*tetrahydropyrimidine* (II).—Distillation of the hydrate under reduced pressure or dehydration using benzene as an entrainer, gives a liquid from which the *base* (II) is obtained by fractionation under reduced pressure (yield, 80%), b. p., 171° (decomp.)/774 mm., 55°/10 mm., 85°/50 mm.; $d_4^{25°}$ 0·8769; $n_D^{25°}$ 1·4561; $[R_L]_D$ 47·8 (Calc., 47·84) (Found: C, 70·3; H, 11·3; N, 18·5; equiv., 77. $C_9H_{18}N_2$ requires C, 70·1; H, 11·7; N, 18·2%; equiv., 77). The liquid is pale yellow and of ammoniacal odour. Addition of water to (II) gave the hydrate in 72% yield. There is some decomposition during the formation of (II), the water removed is strongly ammoniacal, and materials boiling higher than (II) are formed.

Both bases are readily decomposed in aqueous solution. The hydrate (1·72 g.) when boiled with an aqueous solution of oxalic acid (2·52 g.), the water removed on a steam-bath under slightly reduced pressure, and the dry residue extracted with absolute alcohol left ammonium hydrogen oxalate (1·03 g.; theory, 1·07 g.). The alcoholic solution on evaporation gave crude diacetonamine hydrogen oxalate, m. p., 124°, after crystallisation. In another experiment 1·72 g. were boiled with excess of aqueous oxalic acid and the acetone distilling was absorbed in water and estimated by the method of Messenger (Found: 0·57 g. Calc.: 0·58 g.). Attempts were made to benzoylate the hydrate by normal

Schotten–Baumann procedure, in dry pyridine, and in ether in presence of potassium carbonate. The only products identified were benzamide and *N*-benzoyldiacetonamine [m. p. (from alcohol) and mixed m. p. 99—100°].

2 : 2 : 4 : 4 : 6-*Pentamethylhexahydropyrimidine* (IV).—The hydrate (86 g.) was reduced with sodium (40 g.) in alcohol (250 ml.) and the product was first distilled with the alcohol and then separated by fractional distillation. The pure *product* (64 g., 82%) was colourless fuming liquid of sweet, slightly ammoniacal odour. It absorbs carbon dioxide from air and is hygroscopic; b. p., 56·5°/10 mm., 90·5°/50 mm., 172—175° (decomp.)/765 mm.; $d_4^{25°}$ 0·8653, $n_D^{25°}$ 1·4517; $[R_L]_D$ 48·7 [Calc. for (IV), 48·77; for (VII), 49·86] (Found: C, 69·3; H, 12·8; N, 18·2; equiv., 77. $C_9H_{20}N_2$ requires C, 69·3; H, 12·8; N, 18·0%; equiv., 78). Reduction of (II) also yields (IV), but preparation from the hydrate is preferable. Hydrolysis of (IV) with hot water is rapid and in an hour 80% of the calculated amount of acetone was liberated.

Conversion of (IV) *into* 2 : 4-*Diamino-2-methylpentane* (XI).—(IV) (54 g.) was added slowly to 2N-hydrochloric acid (380 ml.) at 0°, and after a day at room temperature the mixture was heated to remove acetone. Sufficient solid sodium hydroxide was added to give a 40% aqueous solution, the diamine layer was separated, and the aqueous liquors were extracted with ether. The *diamine* was dried over potassium hydroxide and barium oxide. Fractional distillation gave a colourless liquid (yield, 33·5 g.; 83%), b. p. 45—46°/10 mm.; $d_4^{25°}$ 0·8312; $n_D^{25°}$ 1·4386; $[R_L]_D$ 36·8 (Calc., 36·75) (Found: C, 62·6; H, 13·5; N, 23·1. $C_6H_{16}N_2$ requires C, 62·1; H, 13·8; N, 24·1%). (XI) was also prepared from diacetonamine by the method of Harries and Adamiantz (*Ber.*, 1901, **34**, 301); b. p. 42—46/10 mm.; $n_D^{18°}$ 1·439; $d_4^{25°}$ 0·836.

The *diacetyl* derivative obtained from (XI) and either acetic anhydride or keten formed colourless crystals from chloroform, m. p., 163° (Found: C, 60·0; H, 10·0; N, 14·2. $C_{10}H_{20}O_2N_2$ requires C, 60·0; H, 10·0; N, 14·0%). The *dibenzoyl* derivative obtained by the Schotten–Baumann procedure from (XI) formed colourless rosettes from alcohol, m. p., 153° (Found: C, 74·2; H, 7·4; N, 8·7. $C_{20}H_{24}O_2N_2$ requires C, 74·1; H, 7·4; N, 8·6%); it showed no depression of melting point with the derivative prepared from the specimen of (XI) synthesised from diacetonamine. This same dibenzoyl derivative is slowly formed when (IV) is benzoylated.

2 : 4-Diamino-2-methylpentane (XI), chloro-2 : 4-dinitrobenzene, sodium acetate, and alcohol were refluxed for 1 hour. The *bis*-2 : 4-*dinitrophenyl* derivative formed yellow crystals from *o*-dichlorobenzene, m. p., 235° (Found: C, 48·3; H, 4·4; N, 18·9. $C_{18}H_{20}O_8N_6$ requires C, 48·2; H, 4·5; N, 18·7%). With like experimental conditions (IV) gave this same compound.

2-*Keto*-4 : 4 : 6-*trimethylhexahydropyrimidine*.—Equimolecular amounts of 2 : 4-diamino-2-methylpentane and urea were heated at 150° for 1 hour. The *product* separated from acetone as white crystals, m. p. 205—206° (Found: C, 59·5; H, 9·7; N, 19·9. $C_7H_{14}ON_2$ requires C, 59·2; H, 9·9; N, 19·7%).

4 : 4 : 6-*Trimethylhexahydropyrimidine* (XII).—The method used by Titherley and Branch (*J.*, 1913, **103**, 334) for hexahydropyrimidine was adopted, and 2 : 4-diamino-2-methylpentane (XI) (2·09 g.) was neutralised with 0·2N-hydrochloric acid, an equal weight of (XI) added, followed by 36% aqueous formaldehyde (3·5 ml.) in 3 hours. After a further 2 hours, potassium hydroxide (60 g.) was added, the *product* extracted with ether, and the solution dried (BaO) and distilled. Yield, 3·3 g.; b. p. 55—57°/10 mm.; $n_D^{18°}$ 1·457 [Found: C, 65·7; H, 12·8; N, 21·7; equiv., 132. $C_7H_{16}N_2$ requires C, 65·7; H, 12·5; N, 21·9%; equiv. (monoacid), 128].

Trimethylhexahydropyrimidine (XII), by Schotten–Baumann procedure, gave its own *NN'*-dibenzoyl derivative, together with 2 : 4-dibenzamido-2-methylpentane. The former being the more soluble, only a partial separation was made by fractional crystallisation from alcohol, and the final separation was made by hand picking. This *dibenzoyl* derivative forms needles, m. p. 156° (Found: C, 75·0; H, 6·9; N, 8·3. $C_{21}H_{24}O_2N_2$ requires C, 74·8; H, 7·1; N, 8·3%).

2 (*or* 4)-*Amino*-4 (*or* 2)-*isopropylamino*-2-*methylpentane* (V) *or* (VI).—This was obtained by reduction of (II), its hydrate, or (IV) with an equal weight of aluminium amalgam in moist ether. The reaction proceeded slowly and was complete after 2 days; the ethereal liquors were then filtered off, and the oxide sludge was washed with ether. When distilling the ethereal liquors the alcohol introduced with the amalgam distilled as a fore-fraction containing much diamine. Yields of pure *diamine* were 60—70% when this fore-fraction was neglected; with recovery from it the yields rose to 85%. Dried over sodium, (VI) forms a colourless hygroscopic liquid, b. p. 178°/760 mm. (no decomp.), 65—67°/10 mm., 104°/65 mm.; $d_{25°}^{25°}$ 0·8130; $n_D^{25°}$ 1·432 (Found: C, 68·4; H, 14·0; N, 17·7; equiv., 81. $C_9H_{22}N_2$ requires C, 68·4; H, 13·9; N, 17·7%; equiv., 79).

The *dihydrochloride*, prepared in dry ether and crystallised from amyl alcohol, had m. p. 250° (decomp.) (Found: Cl, 30·5. $C_9H_{22}N_2,2HCl$ requires 30·7%). The *dibenzoyl* derivative was prepared by the Schotten–Baumann method; crystals from alcohol, m. p. 133° (Found: C, 75·2; H, 8·25; N, 7·8. $C_{23}H_{30}O_2N_2$ requires C, 75·4; H, 8·2; N, 7·6%).

Sufficient chloro-2 : 4-dinitrobenzene was used with sodium acetate in alcohol to substitute both amino-groups, but only one reacted. The 2 : 4-*dinitrophenyl* derivative crystallised from alcohol in orange needles, m. p. 91° (Found: C, 55·6; H, 7·4; N, 17·7. $C_{15}H_{24}O_4N_4$ requires C, 55·6; H, 7·4; N, 17·3%).

2 : 4 : 4 : 6-*Tetramethyl*-2-(2-*amino*isobutyl)-2 : 3 : 4 : 5-*tetrahydropyrimidine* (X).—Mesityl oxide (120 g.) and liquid ammonia (49 g.) were cooled in an autoclave to − 40° and then stirred for 24 hours at room temperature. The autoclave was then cooled again and a further quantity of mesityl oxide (120 g.) and ammonia (26 g.) added. After 6 days at room temperature, the product was removed and cooled to − 40°. The white crystalline solid that separated (58 g.) crystallised from ether in white flakes, m. p. 61—62° [Found: C, 68·0; H, 11·5; N, 19·9; equiv., 71; *M* (in nitrobenzene), 218. $C_{12}H_{26}N_2$ requires C, 68·2; H, 11·8; N, 19·9%; equiv., 70·3; *M*, 211].

This *compound* (X) reacts rapidly with a cold solution of oxalic acid in alcohol, a precipitate of ammonium hydrogen oxalate appearing shortly after the reagents are mixed. From (X) (2·11 g.) and oxalic acid hydrate (3·78 g.) in alcohol (10 ml.) after ½ hour at the b. p., filtration gave ammonium hydrogen oxalate (1·8 g.) and concentration of the filtrate diacetonamine hydrogen oxalate (0·87 g.).

The latter melted at 124—125° after crystallisation (Found: C, 43·0; H, 7·8. Calc. for $C_8H_{17}O_6N$: C, 43·0; H, 7·6%). There were 2·1 g. of uncrystallisable residues.

2 : 4 : 4 : 6-*Tetramethyl*-2-(2-*aminoisobutyl*)*hexahydropyrimidine*.—Reduction of (X) (21 g.) in alcohol (100 ml.) with sodium (10 g.) followed by the addition of water (50 ml.) gave the *product* as an oil, which was dried and fractionally distilled (yield, 12—14 g.). It was a colourless liquid, b. p. 122—125°/10 mm.; $d_{25°}^{25°}$ 0·8668; $n_D^{25°}$ 1·458 (Found: C, 67·4; H, 13·0; N, 20·1; equiv., 72. $C_{12}H_{27}N_3$ requires C, 67·6; H, 12·7; N, 19·7%; equiv., 71).

We wish to thank Mr. D. J. Clark, M.Sc., of these laboratories, for the micro-analyses.

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262. *The Structure of Glycogen. Ratio of Non-terminal to Terminal Glucose Residues.*

By T. G. HALSALL, E. L. HIRST, and J. K. N. JONES.

An assay of the proportion of terminal groups present in various glycogens has been made by measuring the amount of formic acid liberated on oxidation of the polysaccharide by potassium periodate. All the glycogens examined gave results indicating that approximately 12 glucose residues were present per end group, except that certain samples of rabbit-liver glycogen contained approximately 18 residues per end group. The results are in agreement with determinations of the percentage of end groups arrived at by estimation of the tetramethyl glucose produced on hydrolysis of the methylated glycogen.

THE proportion of terminal groups present in samples of glycogen isolated from various sources has been determined previously by methylation of the polysaccharide followed by the quantitative determination of the amount of tetramethyl methyl-*d*-glucoside in the products of methanolysis of the methylated polysaccharide, and in this way it was found that for most samples the ratio of terminal to non-terminal glucose residues was approximately 1 to 12. Nevertheless, in certain samples of rabbit-liver glycogen the ratio was nearer 1 to 18. No completely satisfactory explanation of this variation has yet been put forward, and further investigation was clearly needed. The examination of a large number of samples by the classical methylation technique is a lengthy operation, but starches and glycogens respond readily to the periodic acid oxidation process in which, under carefully standardised conditions, formic acid is liberated quantitatively from the terminal residues of each side chain, and it was decided, therefore, to examine various samples of glycogen by this method (cf. Brown, Dunstan, Halsall, Hirst, and Jones, *Nature*, 1945, **156**, 785; *idem*, *J.*, in the press). In some instances comparative experiments were made by the methylation method, using newly developed semi-micro-methods for the determination of the tetramethyl methylglucoside which arises from each end group (Bell, *J.*, 1944, 473; Jones, *J.*, 1944, 333; Brown and Jones, in the press).

Through the kindness of Dr. D. J. Bell of Cambridge University, we were able to investigate numerous samples of glycogens which he had isolated from various sources. These included glycogen from *Ascaris lumbricoides*, *Mytilus edulis*, human muscle, rabbit liver, rabbit muscle (fasted), and horse muscle. Some of these had already been assayed by him using the methylation procedure. A check was thus provided of the results derived by determination of the formic acid produced after oxidation of the glycogen with potassium periodate. Figures in excellent agreement with those obtained by the use of the methylation procedure were observed. Dr. F. Smith very kindly placed at our disposal samples of guinea-pig-liver glycogen and rabbit-liver glycogen which had been assayed by the methylation technique at Birmingham University.

The proportion of end groups in rabbit-liver glycogen was first determined by Haworth and Percival (*J.*, 1932, 2277) who reported the figure of 1 for every 12 glucose residues. Examination of another sample of rabbit-liver glycogen by Haworth, Hirst, and Isherwood (*J.*, 1937, 577) showed, however, that this glycogen contained approximately 18 glucose residues per end group. This result was confirmed by Bell (*Biochem. J.*, 1936, **30**, 1612) and by Bacon, Baldwin, and Bell (*ibid.*, 1944, **38**, 198) who demonstrated that the ratio of terminal to non-terminal residues in rabbit-liver glycogen may be either 12 to 1 or 18 to 1 approximately, the value observed being apparently dependent upon the carbohydrate diet of the rabbit. We have now confirmed by the periodate oxidation method the higher figure for the sample of rabbit-liver glycogen examined by Haworth, Hirst, and Isherwood, and have obtained also a ratio of 18 to 1 approximately, by both methods of assay, for another sample of rabbit-liver glycogen prepared

by Messrs. Hopkin & Williams Ltd. On the other hand, the sample of rabbit-liver glycogen which had been found by Bell to give the value 12 gave a low value by the periodate method also. Further investigation is clearly required to ascertain the precise reasons for these unpredictable variations which appear to occur only in rabbit-liver glycogen. In all other cases, including those cited in the table and the numerous samples of fish-liver and fish-muscle glycogen examined by Smith (*J.*, 1939, 1915), the value obtained has been 12 approximately.

Experimental

Potassium Periodate Oxidation of Glycogens. General Procedure.—The glycogen (*ca.* 500 mg.) was placed in a 500 ml. stoppered bottle which had been cleaned with chromic acid and steamed out. A known volume of water was added, followed by potassium chloride (5 g.) and a known excess of an aqueous solution of sodium metaperiodate. The oxidations were carried out at 15° with continuous shaking and in dim light (sunlight must be avoided). Portions of the solution (20 ml.) were withdrawn at intervals, excess of ethylene glycol was added, and the formic acid present was estimated by titration with 0·1N-barium hydroxide using a micro-burette and methyl-red as indicator. The resulting titres, after correction when necessary to allow for the slight acidity or alkalinity of the glycogen, were plotted against time to make sure that the normal type of reaction was proceeding, and the acid titre corresponding to 150 hours was used in the calculations, this being the time required for the liberation of 1 mol. of formic acid from β-methyl-*d*-maltoside under these conditions (Halsall, Hirst, and Jones, *J.*, *loc. cit.*). From this titre the size of the repeating unit was calculated. The results are given in the table.

Source of glycogen.	Wt. of glycogen (mg.).	Yield of formic acid (mg.).	Glucose residues per end group. (*a*) By periodate method.	(*b*) By methylation method.
1. *Ascaris lumbricoides*	567	13·5	12	13—14 (*a*)
2. *Mytilus edulis*	510	14·1	10	11 (*b*)
3. Human muscle	518·8	12·9	11	—
4. Rabbit (fasted) muscle	510·5	11·0	13	—
5. Horse muscle	400·4	8·1	14	12 (*c*)
6. Rabbit liver	365·5	7·2	14	12 (*d*)
7. Rabbit liver	509	9·0	16	18 (*e*)
8. Rabbit liver	871	13·8	18	18 (*f*)
9. Rabbit liver	216	4·2	14	12 (*g*)
10. Guinea-pig liver	174·5	3·9	13	12 (*g*)

Glycogens 1—6 were prepared by Dr. D. J. Bell.
Glycogen 7 was a sample of the material used by Haworth, Hirst, and Isherwood (*loc. cit.*).
Glycogen 8 was prepared by Messrs. Hopkin & Williams, Ltd.
Glycogens 9 and 10 were prepared by Dr. F. Smith.

(*a*) Bell, *J.*, 1944, 474.
(*b*) This figure was obtained for another sample examined by Meyer, *Naturwiss.*, 1941, **29**, 287.
(*c*) Bell, *Biochem. J.*, 1935, **29**, 2031.
(*d*) Bell, *Biochem. J.*, 1937, **31**, 1683.
(*e*) Haworth, Hirst, and Isherwood (*loc. cit.*).
(*f*) Present paper.
(*g*) F. Smith (private communication).

Size of Repeating Unit of Rabbit-liver Glycogen (*No.* 8 *in Table*), *by the Methylation Method.*—The glycogen was methylated with methyl sulphate and sodium hydroxide according to the method of Hirst and Young (*J.*, 1939, 1471). The methylated glycogen [759·5 mg.; $[\alpha]_D^{21°}$ + 206° in chloroform (*c*, 8·5); OMe, 45·1%] was hydrolysed with methyl-alcoholic hydrogen chloride (1·5%; 100 ml.) and the amount of 2 : 3 : 4 : 6-tetramethyl methylglucoside in the resulting mixture of glucosides was estimated by the partition method of Brown and Jones (this vol., p. 1344). Yield of 2 : 3 : 4 : 6-tetramethyl methylglucoside, 50·3 mg.; $n_D^{16°}$ 1·4445; $[\alpha]_D^{21°}$ + 66° in water (*c*, 2·3); corresponding to the presence of 18—19 glucose residues per end group.

We wish to thank Mr. L. Hough for assistance in the experimental work, and one of us (T. G. H.) wishes to thank the British Cotton Industry Research Association for the award of a Shirley Research Fellowship.

The University, Manchester. [*Received, December 23rd,* 1946.]

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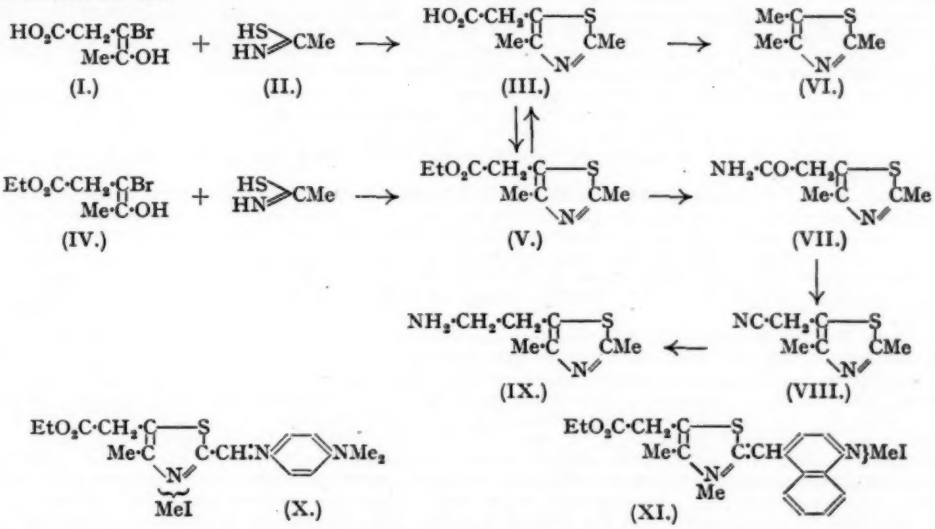
263. *The Conversion of Sucrose into Thiazole Derivatives. Part II. 2 : 4-Dimethylthiazole Derivatives and 2 : 4 : 5-Trimethylthiazole.*

By Hilda Gregory and L. F. Wiggins.

Condensation of β-bromolævulic acid and its ethyl ester with thioacetamide yields 2 : 4-*dimethylthiazole-5-acetic acid* and *ethyl* 2 : 4-*dimethylthiazole-5-acetate* respectively. Several derivatives of the latter product are described, and decarboxylation of 2 : 4-dimethylthiazole-5-acetic acid affords a convenient method for the preparation of 2 : 4 : 5-trimethylthiazole.

SUCROSE can be readily transformed into lævulic acid, and in Part I (this vol., p. 590) we described several sulphanilamidothiazoles, which were obtained through the condensation of β-bromolævulic acid and its ethyl ester with thiourea. Continuing this theme, we have now investigated the condensation of β-bromolævulic acid (I) with thioacetamide (II), whereby **2 : 4-*dimethylthiazole-5-acetic acid hydrobromide*** is obtained; this is readily converted into 2 : 4-dimethylthiazole-5-acetic acid (III). The latter, on esterification, gave ethyl 2 : 4-dimethylthiazole-5-acetate (V), identical with the product of the condensation of ethyl β-bromolævulate (IV) with thioacetamide.



Decarboxylation of 2 : 4-dimethylthiazole-5-acetic acid was effected smoothly to give an 80% yield of 2 : 4 : 5-trimethylthiazole (VI). Hitherto, this trimethylthiazole has only been prepared by the condensation of thioacetamide with methyl 1-chloroethyl ketone (Roubleff, *Annalen*, **1890**, **259**, 258).

Treatment of the thiazole ester with concentrated aqueous ammonia gave the corresponding *amide* (VII) which was readily dehydrated with phosphorus oxychloride to **2 : 4-*dimethyl-5-cyanomethylthiazole*** (VIII). The latter, on catalytic hydrogenation over Raney nickel, was converted into 2 : 4-dimethyl-5-2′-aminoethylthiazole (IX) which, however, was unstable and could only be isolated as the *dipicrate*. In view of the previous work of Hinegardner and Johnson (*J. Amer. Chem. Soc.*, **1930**, **52**, 3724), this compound should exhibit some physiological activity as a sympathomimetic agent.

It has been shown previously by Mills and Smith (*J.*, **1922**, **121** 2724) that the activity of the substituent methyl group in the thiazole ring depends upon its position. Thus, whereas 4-phenyl-2-methylthiazole will condense readily with benzaldehyde and phthalic anhydride, and its quaternary ammonium salts couple with *p*-dimethylaminobenzaldehyde, its isomer, 2-phenyl-4-methylthiazole, undergoes none of these reactions. In this work we found that *ethyl* **2 : 4-*dimethylthiazole-5-acetate methiodide*** underwent reaction with only 1 mole of *p*-nitrosodimethylaniline to form **4-*methyl-5-carbethoxymethylthiazole-2-aldehyde* p-*dimethylaminoanil methiodide*** (X) which was a brownish-green crystalline compound with a bluish-green metallic reflex, giving rise to deep purple aqueous solutions. Similarly, ethyl 2 : 4-dimethylthiazole-5-acetate methiodide condensed with 1 mole of quinoline methiodide to give a deep red crystalline compound which, by analogy to 4-phenyl-3-methyl-2-thiazolenyl-4-quinolylmethane methiodide of Mills and Smith (*loc. cit.*), must be **3 : 4-*dimethyl-5-carbethoxymethyl-2-thiazolenyl-4-quinolylmethane methiodide*** (XI).

EXPERIMENTAL.

Ethyl **2 : 4-*Dimethylthiazole-5-acetate.***—To ethyl β-bromolævulate (20·8 g.) dissolved in ethyl alcohol (20 c.c.), thioacetamide (7·0 g.) was slowly added in small portions; an exothermic reaction occurred with formation of a yellow solution. After 12 hours at room temperature, the alcohol was removed and the thick yellow syrup thus obtained dissolved in water, a few drops of hydrochloric acid (5N) were added, and the solution was extracted with ether to remove any unchanged starting materials. Ammonia (5N) was added to the aqueous solution at 0° until the solution was slightly alkaline (litmus);

a yellow oil then separated. The crude product was extracted with ether, and the ethereal layer was washed with water and dried ($MgSO_4$), and the ether removed. The residual liquid was distilled in a vacuum; *ethyl* 2 : 4-*dimethylthiazole* 5-*acetate* was thus obtained as a pale yellow liquid, b. p. 142°/15 mm, 212°/756 mm., $n_D^{18°}$ 1·4942. Yield, 11·6 g. (62·5%) (Found: C, 53·9; H, 6·1; N, 7·2; OEt, 23·1. $C_9H_{13}O_2NS$ requires C, 54·2; H, 6·5; N, 7·0; OEt, 22·6%). The *picrate* was obtained as a yellow, crystalline solid, m. p. 168° (Found: C, 42·4; H, 3·4; N, 13·1. $C_{15}H_{16}O_9N_4S$ requires C, 42·1; H, 3·7; N, 13·1%).

Condensation of β-Bromolævulic Acid with Thioacetamide.—Thioacetamide (1·0 g.) was added in portions to β-bromolævulic acid (2·25 g.) at 80°. After a few minutes, an exothermic reaction occurred, and when the mixture had cooled to room temperature, a partly solid product was obtained. This was pressed on a porous pile, and colourless crystals isolated, which were recrystallised from acetone–ethyl alcohol–light petroleum (b. p. 40—60°). After two recrystallisations, pure 2 : 4-*dimethylthiazole*-5-*acetic acid hydrobromide* was obtained as colourless crystals, m. p. 183°. Yield, 1·78 g. (61·2%) (Found: C, 33·7; H, 4·3. $C_7H_{10}O_2NBrS$ requires C, 33·4; H, 4·0%).

The free base was obtained from the hydrobromide (1·5 g.) by dissolving it in water (6 c.c.) and heating under reflux for 15 minutes. The strongly acid solution was cooled, and a concentrated aqueous solution of potassium hydroxide added carefully, until, when the solution was still acid to litmus, crystals separated. These were filtered off and recrystallised from hot water; m. p. 185°. Yield, 0·93 g. (91·4%).

Esterification of 2 : 4-*Dimethylthiazole*-5-*acetic Acid.*—The acid (2·0 g.) was heated under reflux with 2% ethyl-alcoholic hydrogen chloride (50 c.c.) for 6 hours. The resulting solution was neutralised with barium carbonate, the barium salts were filtered off, and the alcoholic solution was evaporated to dryness under reduced pressure. The residue was extracted with ether, and the ethereal extract evaporated to a brown liquid which was subsequently distilled; b. p. 212°/745 mm., $n_D^{20°}$ 1·4943 (Found: OEt, 22·9. Calc. for $C_9H_{13}O_2NS$: OEt, 22·6%). Yield of ethyl 2 : 4-dimethylthiazole-5-acetate, 1·46 g. (62·7%).

2 : 4 : 5-*Trimethylthiazole.*—2 : 4-Dimethylthiazole-5-acetic acid (0·8 g.) was heated on an oil-bath in a distillation flask. At 190° (bath temp.) the crystals melted; at 235° (bath temp.) carbon dioxide was evolved and a colourless, pungent smelling liquid distilled, b. p. 164—166° (vapour temp.), $n_D^{18°}$ 1·5060. Yield of 2 : 4 : 5-trimethylthiazole, 0·49 g. (82·5%). On treatment with one mol. of picric acid, yellow needles of 2 : 4 : 5-trimethylthiazole picrate were obtained, m. p. 133—134° (Found: C, 40·4; H, 3·7. Calc. for $C_{12}H_{12}O_7N_4S$: C, 40·4; H, 3·4%). Roubleff (*loc. cit.*) gives m. p. 133°.

2 : 4-*Dimethylthiazole*-5-*acetamide.*—Ethyl 2 : 4-dimethylthiazole-5-acetate (1·0 g.) was suspended in concentrated ammonia solution (*d* 0·88; 5 c.c.), and the mixture shaken for 2 hours; a clear yellow solution was then obtained. After several hours at 0°, colourless needles separated. More crystals were obtained by concentration of the mother liquors. The total crude product recrystallised from ethyl alcohol–ether in feathery, colourless needles of 2 : 4-*dimethylthiazole*-5-*acetamide*, m. p. 173°. Yield, 0·72 g. (84·3%) (Found: C, 49·4; H, 5·5; N, 17·1. $C_7H_{10}ON_2S$ requires C, 49·4; H, 5·9; N, 16·5%). On treatment with picric acid, long needles of the *picrate* were obtained, m. p. 185° (Found: C, 39·4; H, 3·5; N, 17·4. $C_{13}H_{13}O_8N_5S$ requires C, 39·1; H, 3·3; N, 17·5%).

2 : 4-*Dimethyl*-5-*cyanomethylthiazole.*—2 : 4-Dimethylthiazole-5-acetamide (1·3 g.) was heated with phosphorus oxychloride (freshly distilled; 5 c.c.) on an oil-bath for 45 minutes at 105—115°. The phosphorus oxychloride was then removed on a water-bath at 50° under reduced pressure. To the dark syrupy residue, crushed ice was added, then solid sodium carbonate until the solution was alkaline (litmus). The dark brown solution was then exhaustively extracted with ether, the ethereal extract dried ($MgSO_4$), and the ether removed by evaporation. The crystalline residue was recrystallised from hot water to give needles of 2 : 4-*dimethyl*-5-*cyanomethylthiazole*, m. p. 87°. Yield, 1·0 g. (86%) (Found: C, 54·9; H, 4·9; N, 17·8. $C_7H_8N_2S$ requires C, 55·3; H, 5·2; N, 18·1%). The *picrate* was obtained as a yellow crystalline solid, m. p. 125° (Found: C, 40·9; H, 3·2. $C_{13}H_{11}O_7N_5S$ requires C, 40·9; H, 2·9%).

Reduction of 2 : 4-*Dimethyl*-5-*cyanomethylthiazole.*—2 : 4-Dimethyl 5-cyanomethyl thiazole (0·95 g.) was dissolved in methyl alcohol (40 c.c.) and hydrogenated over Raney nickel at room temperature. When approximately the theoretical amount of hydrogen had been absorbed and no further absorption occurred, the catalyst was filtered off and the methyl alcohol evaporated under reduced pressure in an atmosphere of nitrogen. The product decomposed on keeping but was characterised as the dipicrate. A solution of the syrup (0·2 g.) in alcohol was added to a hot concentrated aqueous solution of picric acid (0·6 g.). On cooling, an oil separated, which eventually solidified and recrystallised from hot water In yellow crystals, m. p. 169°. It was 2 : 4-*dimethyl*-5-2′-*aminomethylthiazole dipicrate* (Found: C, 37·3; H, 3·0; N, 17·9. $C_{19}H_{18}O_{14}N_8S$ requires C, 37·1; H, 2·9; N, 18·2%).

Condensation of Ethyl 2 : 4-*Dimethylthiazole*-5-*acetate Methiodide with* p-*Nitrosodimethylaniline.*—Ethyl 2 : 4-dimethylthiazole-5-acetate (1·0 g.) was kept with methyl iodide (100% excess) at room temperature for 24 hours. The methyl iodide was then evaporated under reduced pressure. A yellow oil was obtained which slowly crystallised; it recrystallised from alcohol in colourless prisms, m. p. 133°, which decomposed too rapidly for analytical figures to be obtained.

To an alcoholic solution of ethyl 2 : 4-dimethylthiazole-5-acetate methiodide (crude oil; 1·0 g.) was added on alcoholic solution of *p*-nitrosodimethylaniline (0·5 g.), whereby a bright green solution was obtained. Piperidine (2 drops) was added; the colour changed to reddish brown, and the solution was heated under reflux for 15 minutes; a purple colouration had then developed. On cooling, crystals separated and were filtered off (0·3 g.). The solution was again heated for a further 2 hours, and on cooling, more crystals were obtained (0·2 g.). The crude product was recrystallised from aqueous methyl alcohol, and 4-*methyl*-5-*carbethoxymethylthiazole*-2-*aldehyde* p-*dimethylaminoanil methiodide* was obtained as a brownish-green crystalline compound with a bluish-green metallic reflex, m. p. 208°. In dilute aqueous or alcoholic solution the crystals gave a deep purple colouration, which was easily discharged by acids and regenerated by alkali (Found: C, 45·9; H, 5·5. $C_{18}H_{24}O_2N_3IS$ requires C, 45·7; H, 5·1%).

Condensation of Ethyl 2 : 4-Dimethylthiazole-5-acetate Methiodide with Quinoline Methiodide.—To ethyl 2 : 4-dimethylthiazole-5-acetate methiodide (crude oil; 1·0 g.) dissolved in ethyl alcohol (10 c.c.) was added an alcoholic solution of quinoline methiodide (1·7 g.; 100% excess) and sodium hydroxide (0·17 g.). The solution was heated under reflux for 30 minutes; a vivid red colouration had then developed. On cooling, a semi-solid product separated, which was recrystallised from methyl alcohol to give 3 : 4-*dimethyl-5-carbethoxymethyl-2-thiazolenyl-4-quinolylmethane methiodide* as dark red crystals with a bright green, metallic reflex, m. p. 200°. Yield, 0·35 g. (Found: C, 50·3; H, 5·1; N, 6·2. $C_{20}H_{23}O_2N_2IS$ requires C, 49·8; H, 4·8; N, 5·8%).

The authors wish to express their thanks to Professors W. N. Haworth, F.R.S., and J. L. Simonsen, F.R.S., for their interest, and to the Colonial Products Research Council for financial support.

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264. *Anhydrides of Polyhydric Alcohols. Part VII.* 1 : 4-3 : 6-*Dianhydro*-d- *and* -l-*iditol.*

By L. F. WIGGINS.

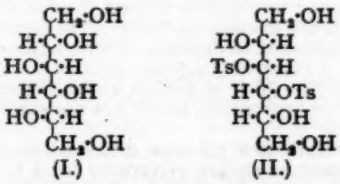
l-Iditol readily undergoes anhydride formation on being heated in the presence of hydrochloric acid, giving 1 : 4-3 : 6-dianhydro-*l*-iditol the structure of which is proved by a constitutional synthesis of its enantiomorph.

THE action of acidic reagents on both mannitol and sorbitol gives rise to the dianhydrides of these polyhydric alcohols by internal loss of two molecules of water. Dianhydromannitol, first obtained by Fauconier (*Compt. rend.*, 1882, **95**, 991), was shown to possess the constitution of 1 : 4-3 : 6-dianhydromannitol by Wiggins in Part I of this series (*J.*, 1945, 4) and by Hockett, Fletcher, Sheffield, Goepp, and Soltzberg (*J. Amer. Chem. Soc.*, 1946, **68**, 930). Dianhydrosorbitol, prepared in a similar way to its mannitol analogue, was shown by synthetical methods (Wiggins and Montgomery, *Nature*, 1946, **157**, 372; *J.*, 1946, 390) also to have the 1 : 4-3 : 6-ring structure. Hockett, Fletcher, Sheffield, and Goepp (*J. Amer. Chem. Soc.*, 1946, **68**, 927) have arrived at the same conclusions by different methods.

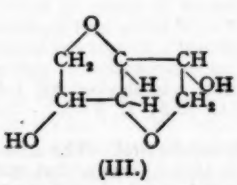
l-Iditol (I) also undergoes a similar dehydration on being heated in the presence of acids and gives a dianhydride, in the form of a *hemihydrate* which, like the corresponding compounds of mannitol and sorbitol, is stable to treatment with sodium methoxide at 120° under pressure. The *bismethanesulphonyl* and the *dibenzoyl* derivative were readily obtained from it.

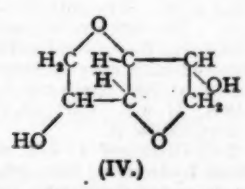
By analogy with the dianhydrides of mannitol and sorbitol it would be expected that this compound would also have the hydrofuranol type of ring structure shown in (III). After the completion of this work, Fletcher and Goepp (*J. Amer. Chem. Soc.*, 1945, **67**, 1042; 1946, **68**, 939) reported that 1 : 4-3 : 6-dianhydrosorbitol and dianhydromannitol on dehydrogenation with Raney nickel followed by hydrogenation are both partly converted into dianhydroiditol, and on the assumption that the rings are stable under these conditions, have declared the establishment of the 1 : 4-3 : 6-ring structure for all three hexitol dianhydrides. The present paper is concerned with a proof of constitution of the dianhydroiditol along quite different lines. A preliminary note of this appeared in *Nature* (1946, **157**, 372).

If mannitol could be tosylated at C_3 and C_4 to give 3 : 4-ditosyl mannitol (II), this compound on removal of the tosyl groups with sodium methoxide could form only two dianhydrides, (*a*) 1 : 3-4 : 6-dianhydrohexitol, and (*b*) 1 : 4-3 : 6-dianhydrohexitol. Moreover, since it is established in the sugar series that, when hydrolytic removal of tosyl groups is accompanied by anhydro-ring formation, Walden inversion always accompanies the hydrolysis (see Peat, *Ann. Reports*, 1939, **36**, 258), it follows that both (*a*) and (*b*) would have the configuration of *d*-iditol.


(I.)

(II.)


(III.)


(IV.)

A suitable derivative substituted at C_3 and C_4 with tosyl residues is 3 : 4-ditosyl 1 : 2-5 : 6-diacetone mannitol (Brigl and Gruner, *Ber.*, 1934, **67**, 1969). This compound, on partial hydrolysis

followed by acetylation, gave liquid 3 : 4-*ditosyl* 1 : 2 : 5 : 6-*tetra-acetyl mannitol* which on treatment with sodium methoxide gave a crystalline dianhydrohexitol which gave crystalline bismethanesulphonyl and dibenzoyl derivatives. These had the same melting points as and specific rotation equal, but opposite in sign, to the corresponding derivatives obtained from the product of the anhydridisation of *l*-iditol. Therefore the two sets of compounds are enantiomorphous, and *dianhydro*-d-*iditol* and *bismethanesulphonyl* and *dibenzoyl dianhydro*-d-*iditol* must have been obtained from mannitol.

The precise constitution of dianhydroiditol is limited to the possibilities (*a*) and (*b*) above. Since (*a*) involves four-membered rings which are extremely unlikely of formation when five-membered rings are possible, and since in (*a*) the two free hydroxyl groups would approach near enough to be joined in acetal formation by a benzylidene residue, and because dianhydroiditol does not form such a derivative, structure (*b*) must be regarded as the correct one. Dianhydro-*d*-iditol is formulated by (III), a representation differing from that of 1 : 4-3 : 6-dianhydro-*d*-mannitol (IV) only in the orientation of the two rings.

Experimental.

l-*Iditol*.—This was prepared from *l*-sorbose by catalytic hydrogenation and separated from the accompanying *l*-sorbitol by fractional crystallisation of the acetyl derivatives (Jones and Wiggins, *J.*, 1944, 363).

Action of Hydrochloric Acid on l-*Iditol*.—Crystalline *l*-iditol (5 g.) was boiled under reflux for 50 hours with fuming hydrochloric acid (50 c.c.). The dark brown solution was evaporated to a syrup which was distilled at 150—155° (bath temp.)/0·05 mm. The distillate (3·1 g.) crystallised completely on cooling. It recrystallised in prisms from ethyl acetate (2·3 g.), m. p. 43—45°, $[\alpha]_D^{17°}$ + 18·4° (*c*, 2·389 in water), and was 1 : 4-3 : 6-*dianhydro*-l-*iditol hemihydrate* (Found: C, 46·7, 46·1; H, 7·0, 7·3. $C_6H_{10}O_4.\frac{1}{2}H_2O$ requires C, 46·5; H, 7·1%).

Treatment of Dianhydro-l-*iditol with Sodium Methoxide*.—The dianhydroiditol (1·7 g.) was heated in a sealed tube with 5% methyl-alcoholic sodium methoxide at 120° for 24 hours. Thereafter, the solution was diluted with water, neutralised with sulphuric acid, and evaporated to dryness, and the residue was extracted with ethyl acetate. The extract was evaporated and the syrupy product distilled at 160°/0·02 mm. The distillate, which completely crystallised, was unchanged 1 : 4-3 : 6-dianhydro-*l*-iditol (1·55 g.); it recrystallised from ethyl acetate as the hemihydrate, m. p. 43—45° alone or in admixture with the starting material.

Attempted Condensation of Dianhydro-l-*iditol with Benzaldehyde*.—The dianhydride (0·55 g.) was shaken with freshly distilled benzaldehyde (10 c.c.) and zinc chloride (0·5 g.) for 48 hours. The resulting suspension was poured into water–ligroin which completely dissolved it. Sodium carbonate (0·5 g.), dissolved in water, was added and the mixture distilled under reduced pressure, with addition of water until all the benzaldehyde was removed. After being evaporated to dryness the residue was extracted with ethyl acetate, and the extract evaporated. From ethyl acetate there crystallised unchanged dianhydro-*l*-iditol hemihydrate (0·4 g.), m. p. 43—45° alone or in admixture with the starting material.

2 : 5-*Bismethanesulphonyl* 1 : 4-3 : 6-*Dianhydro*-l-*iditol*.—The dianhydride (0·2 g.), dissolved in dry pyridine (5 c.c.), was treated with methanesulphonyl chloride (0·4 g.) at room temperature. The mixture was kept for 24 hours and then poured into ice–water. The crystalline precipitate was collected; the *compound* recrystallised from alcohol in long needles, m. p. 155—156°, $[\alpha]_D^{17°}$ + 41·9° (*c*, 1·145 in acetone) (Found: C, 32·2; H, 4·9. $C_8H_{14}O_8S_2$ requires C, 31·8; H, 4·6%).

2 : 5-*Dibenzoyl Dianhydro*-l-*iditol*.—The dianhydride (0·1 g.) was dissolved in 5N-sodium hydroxide (3 c.c.), and benzoyl chloride (0·3 g. added). After vigorous shaking for ½ hour, the solid which had separated was collected and washed with water; the *compound* recrystallised from alcohol in plates (0·13 g.), m. p. 110—111°, $[\alpha]_D^{15°}$ +139·1° (*c*, 1·04 in chloroform) (Found: C, 67·7; H, 4·9. $C_{20}H_{18}O_6$ requires C, 67·8; H, 5·1%).

3 : 4-*Ditosyl Tetra-acetyl Mannitol*.—3 : 4-Ditosyl 1 : 2-5 : 6-diacetone mannitol (10 g.) (prepared by the method of Brigl and Gruner, *loc. cit.*) was hydrolysed by heating it for 3 hours at 70° with 70% acetic acid (100 c.c.). The acetic acid was removed under reduced pressure. The resulting syrup was acetylated by boiling with acetic anhydride (26 c.c.) and sodium acetate (10 g.). The mixture was poured into water and the product neutralised with sodium bicarbonate and extracted with chloroform. The extract was dried ($MgSO_4$) and evaporated. The *compound* was a syrup (7·5 g.) which could not be induced to crystallise; $[\alpha]_D^{18°}$ − 0·8° (*c*, 10·23 in chloroform) (Found: S, 9·6. $C_{28}H_{34}O_{14}S_2$ requires S, 9·7%).

Treatment of 3 : 4-*Ditosyl Tetra-acetyl Mannitol with Sodium Methoxide*.—The syrup (7·5 g.) was dissolved in chloroform (100 c.c.), and sodium methoxide (4 g.), dissolved in dry methyl alcohol (40 c.c.), added at 0°. The mixture was allowed to warm up to room temperature and to remain thereat for 4 hours. The mixture was extracted with water and separated from the chloroform layer. The aqueous extract was neutralised with N-sulphuric acid and the solution evaporated to dryness. The residue was extracted with ethyl acetate, and on evaporation of this solvent a syrup (0·9 g.) was obtained. This distilled at 160° (bath temp.)/0·08 mm. and showed $n_D^{16°}$ 1·4925, $[\alpha]_D^{18°}$ − 16·7° (*c*, 5·27 in water) (Found: C, 48·8; H, 6·8. $C_6H_{10}O_4$ requires C, 49·3; H, 6·8%). The *product* crystallised but it was not possible to recrystallise it.

2 : 5-*Dibenzoyl* 1 : 4-3 : 6-*Dianhydro*-d-*iditol*.—The above distillate (0·8 g.) was dissolved in 5N-sodium hydroxide; benzoyl chloride (2 c.c.) was added, and the mixture shaken vigorously for ½ hour. The *dibenzoyl* derivative was collected, washed with water, and recrystallised from alcohol. Yield, 0·94 g.; m. p. 110—111°; $[\alpha]_D^{15°}$ − 138·6° (*c*, 3·475 in chloroform) (Found: C, 68·0; H, 5·2. $C_{20}H_{18}O_6$ requires C, 67·8; H, 5·1%).

2 : 5-*Bismethanesulphonyl* 1 : 4-3 : 6-*Dianhydro*-d-*iditol*.—Dianhydro-*d*-iditol (0·3 g.) was dissolved in dry pyridine (6 c.c.) and methanesulphonyl chloride (0·8 g.) added at 0°. The mixture was kept at room temperature for 74 hours and was then poured into ice–water, and the solid which had separated was collected and washed with water; the *compound* recrystallised from alcohol in the form of needles. Yield, 0·25 g.; m. p. 156°; $[\alpha]_D^{15°}$ − 41·2° (*c*, 1·41 in acetone) (Found: C, 32·1; H, 4·3. $C_8H_{14}O_8S_2$ requires C, 31·8; H, 4·6%).

Fletcher and Goepp (*loc. cit.*) give, for anhydrous dianhydro-*l*-iditol, m. p. 63·7—64·5°, $[\alpha]_D$ + 20·8° (in water), and for the dibenzoate, m. p. 111—111·3°, $[\alpha]_D$ + 141·9° (in chloroform).

The author is grateful to Sir Norman Haworth, F.R.S., for his interest in this work, and to the Colonial Products Research Council for financial aid.

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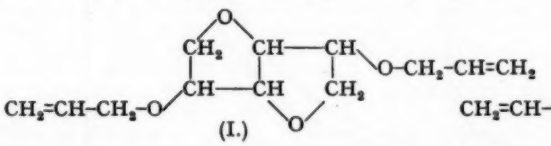
265. *Anhydrides of Polyhydric Alcohols. Part VIII. Some Alkenyl Ethers of* 1 : 4-3 : 6-*Dianhydromannitol and* 1 : 4-3 : 6-*Dianhydrosorbitol.*

By HILDA GREGORY and L. F. WIGGINS.

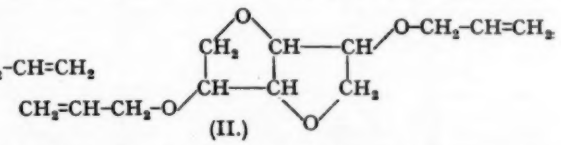
Diallyl and dimethallyl ethers of the 1 : 4-3 : 6-dianhydrides of mannitol and sorbitol have been prepared. They polymerise slowly in a stream of oxygen, the allyl at a greater rate than the methallyl ethers.

IN continuation of our studies of 1 : 4-3 : 6-dianhydro-mannitol and -sorbitol described in Parts I and IV—VII of this series, we have sought to obtain unsaturated ethers of these compounds. In a previous communication (Haworth, Gregory, and Wiggins, *J.*, 1946, 488) we have described unsaturated acyl derivatives of these dianhydrides, namely the diacrylyl and dimethacrylyl esters, which were found to polymerise very rapidly to glass-like resins; saturated ether derivatives have also been reported (Haworth and Wiggins; Patent Application 1945).

The allyl ethers of certain carbohydrates have recently been obtained by Nichols and Yanovsky and their associates; these include allyl sucrose (Nichols and Yanovsky, *J. Amer. Chem. Soc.*, 1945, **67**, 47), tetra-allyl α-methylglucoside (*idem, ibid.*, 1944, **66**, 1625), and allyl starch (Nichols, Hamilton, Smith, and Yanovsky, *Ind. Eng. Chem.*, 1945, **37**, 206). By treating 1 : 4-3 : 6-dianhydro-mannitol and -sorbitol with allyl bromide and concentrated sodium hydroxide solution according to the procedure of Nichols and Yanovsky, we have obtained 2 : 5-*diallyl* 1 : 4-3 : 6-*dianhydromannitol* (I) and 2 : 5-*diallyl* 1 : 4-3 : 6-*dianhydrosorbitol* (II), complete allylation being accomplished in one treatment, giving 70% yields of the



(I.)



(II.)

products. Both compounds were yellow liquids, quite stable to distillation. Although they polymerised slowly in a stream of oxygen, no appreciable effect was observed on heating them in the presence of benzoyl peroxide, a fact previously noted by Nichols and Yanovsky for tetra-allyl α-methylglucoside. The rates of polymerisation of the dianhydrohexitol derivatives at 97° have been followed viscometrically in an Ostwald viscometer modified as shown in Fig. 1, so that oxygen could be bubbled through the substance and the viscosity measured in the same apparatus.

Preliminary experiments showed that the rate of polymerisation depended upon the rate of flow of oxygen through the apparatus, hence the flow of gas was kept constant throughout the polymerisation. It was found that the rate of polymerisation as measured by the viscosity for both the mannitol and the sorbitol derivatives (see Fig. 2) followed closely the behaviour of tetra-allyl α-methylglucoside, described by Nichols and Yanovsky (*loc. cit.*). Fig. 2 shows that the polymerisation of the mannitol derivative was very slightly faster than that of its sorbitol analogue. Both liquids became darker at the beginning of the heating, but became progressively lighter in colour as the polymerisation continued. The viscosity increased slowly for about 180 minutes, followed by a rapid increase to the gelation point, at which the substances were almost colourless. Both end-products were soft and rubbery, completely infusible and insoluble.

On treatment of dianhydromannitol with methallyl chloride and concentrated sodium hydroxide solution at ordinary pressures, 2 : 5-*dimethallyl* 1 : 4-3 : 6-*dianhydromannitol* was obtained in poor yield, owing probably to loss of reagent and incompletion of reaction. Some improvement was effected by carrying out the reaction in an autoclave fitted with a stirring device, and by this method 2 : 5-*dimethallyl*-1 : 4-3 : 6-*dianhydrosorbitol* was obtained. Both of the methallyl derivatives were yellow liquids which polymerised slowly on being heated in a stream of oxygen. Neither, however, gelatinised, or reached a state of acetone insolubility, as distinct from the behaviour of the corresponding allyl derivatives. The rates of polymerisation (see Fig. 2) when investigated under the same conditions as described previously were also markedly slower than those of the allyl ethers; even after 24 hours at 97° in a stream of oxygen at 10 l./hour, no gel formation had occurred and the viscous liquid remained acetone soluble.

FIG. 1.

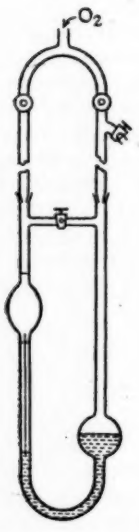
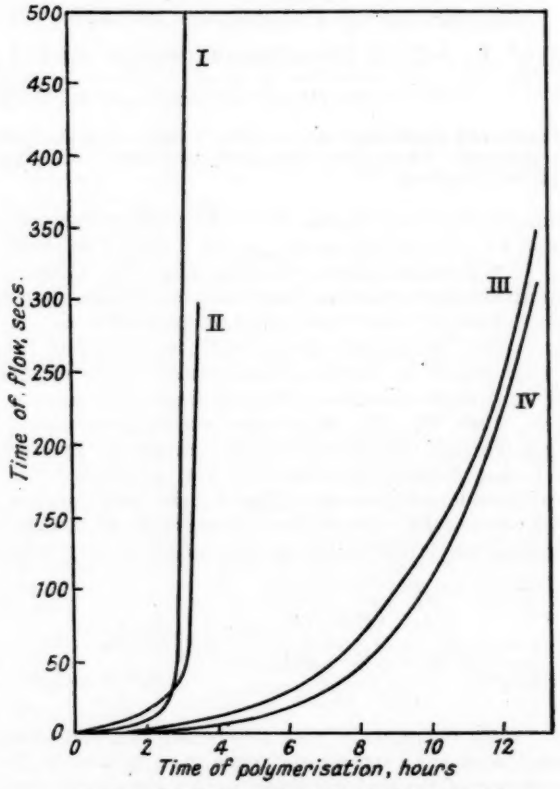


FIG. 2.



I. 2 : 5-*Diallyl* 1 : 4-3 : 6-*dianhydromannitol.*
II. 2 : 5-*Diallyl* 1 : 4-3 : 6-*dianhydrosorbitol.*
III. 2 : 5-*Dimethallyl* 1 : 4-3 : 6-*dianhydrosorbitol.*
IV. 2 : 5-*Dimethallyl* 1 : 4-3 : 6-*dianhydromannitol.*

The difference in the rates of polymerisation of the allyl and methallyl ethers and the difference in properties of the final product must be due to the presence of the methyl group. Therefore, since the methallyl ethers polymerise more slowly and to a lesser degree than the allyl ethers, the methyl group must exhibit an inhibitory effect upon polymerisation. This tendency has been observed previously in many cases. For instance, whereas styrene will undergo addition polymerisation very rapidly, to form long-chain macromolecules, α-methylstyrene will only form an octamer (Staudinger and Breusch, *Ber.*, 1929, **62**, 442), and β-methylstyrene, dimeric molecules (Errera, *Gazzetta*, 1884, **14**, 504).

EXPERIMENTAL.

2 : 5-*Diallyl* 1 : 4-3 : 6-*Dianhydrosorbitol.*—Dianhydrosorbitol (50 g.) was suspended in allyl bromide (85 c.c.) in a three-necked bolthead flask, fitted with a dropping funnel, condenser, and mechanical

stirring device. The well-stirred reaction mixture was maintained at 70°. Sodium hydroxide solution (53 c.c. of a 52% solution, w/v) was added slowly during 1·25 hours, and stirring continued for a further 1·75 hours. Water (100 c.c.) was then added, and any unsaturated volatile compounds present were removed by steam distillation. The mixture was then extracted with ether, the ethereal extract washed with water and dried ($MgSO_4$), and the ether removed, leaving a light brown, mobile liquid. This was fractionally distilled under reduced pressure in an atmosphere of carbon dioxide. The bulk distilled at 157—161°/20 mm. One further distillation gave pure *diallyl dianhydrosorbitol* as a colourless liquid in 70·3% yield, b. p. 185°/40 mm., $n_D^{21°}$ 1·4812, $[\alpha]_D^{22°}$ + 93·4° (*c*, 1·756 in chloroform) (Found : C, 63·4; H, 7·7. $C_{12}H_{18}O_4$ requires C, 63·6; H, 8·0%).

The rate of polymerisation of 2 : 5-diallyl dianhydrosorbitol was followed viscometrically. The results below give the time of flow in seconds for the corresponding time of polymerisation in minutes (in parentheses) : 1·9 (0); 2·4 (20); 2·8 (45); 18 (130); 37·0 (166); 118·0 (196); 160 (205); 245·0 (210); ∞ (216). During the last reading the material gelled in the tube. These results are shown graphically in Fig. 2.

2 : 5-*Diallyl* 1 : 4-3 : 6-*Dianhydromannitol.*—This was prepared on the same scale and in the same way as its sorbitol analogue. The *compound* was obtained as a colourless, mobile liquid, b. p. 173°/10 mm., $n_D^{21°}$ 1·4847, $[\alpha]_D^{23°}$ + 160·3° (*c*, 1·51 in chloroform) (Found : C, 63·2; H, 8·3. $C_{12}H_{18}O_4$ requires C, 63·6; H, 8·0%).

The rate of polymerisation of 2 : 5-diallyl dianhydromannitol was investigated viscometrically. The following results give the time of flow in seconds for the corresponding time of polymerisation in minutes (in parentheses) : 1·4 (0); 1·8 (20); 2·4 (80); 5·6 (105); 15·1 (135); 32·4 (155); 82·0 (170); 120·0 (180); 495·2 (185); ∞ (193). These results are shown graphically in Fig. 2.

2 : 5-*Dimethallyl* 1 : 4-3 : 6-*Dianhydromannitol.*—A mixture of 1 : 4-3 : 6-dianhydromannitol (20·0 g.), methallyl chloride (100 c.c.), and sodium hydroxide (22 c.c. of a 52% solution, w/v) was heated on a boiling water-bath for 10 hours. The mixture was kept well stirred throughout the reaction to prevent the conversion of methallyl chloride into *iso*butaldehyde as a result of the development of local acidity. The mixture was then cooled, water (200 c.c.) was added, and the two layers were separated. The upper layer was dried ($CaCl_2$) and distilled on a boiling water-bath under reduced pressure to remove the more volatile components. The residual oil was fractionally distilled under reduced pressure in an atmosphere of carbon dioxide. The bulk distilled at 132—135°/10 mm. as a pale yellow liquid which darkened on standing. One further distillation under the same conditions gave 2 : 5-*dimethallyl* 1 : 4-3 : 6-*dianhydromannitol* (4·62 g.), b. p. 135°/10 mm., $n_D^{19°}$ 1·4979, $[\alpha]_D^{20°}$ + 71·4° (*c*, 1·168 in chloroform) (Found : C, 66·0; H, 8·3. $C_{14}H_{22}O_4$ requires C, 66·1; H, 8·6%). The rate of polymerisation of 2 : 5-dimethylallyl 1 : 4-3 : 6-dianhydromannitol was investigated viscometrically. The following results give the time of flow in seconds for the corresponding time of polymerisation in minutes (in parentheses) : 2·5 (0); 3·0 (60); 4·0 (120); 2 (150); 5·8 (195); 8·0 (240); 11·2 (300); 18·0 (360); 27·8 (420); 35·0 (450); 52·2 (480); 1400 (990). Further readings could not be taken owing to the high viscosity of the liquid. These results are shown graphically in Fig. 2.

2 : 5-*Dimethallyl* 1 : 4-3 : 6-*Dianhydrosorbitol.*—Dianhydrosorbitol (20 g.), methallyl chloride (100 g.), sodium hydroxide solution (22 c.c. of a 50% solution, w/v), and acetone (100 c.c.) were heated in a stainless steel autoclave, fitted with a stirring device, for 10 hours at 120°. The contents of the autoclave were then diluted with water (200 c.c.) and the mixture was steam distilled to remove acetone, methallyl chloride, and any methallyl alcohol and dimethallyl ether produced during the reaction. The remaining liquid was then cooled and extracted with ether, the ethereal extract was washed with water and dried ($MgSO_4$), and the ether was removed. The residual brown mobile liquid was fractionally distilled under reduced pressure in an atmosphere of carbon dioxide, whereby a pale yellow liquid was obtained, b. p. 150—160°/15 mm. The distillate was then redistilled using the same precautions; *dimethallyl dianhydrosorbitol* (6·4 g.) was obtained, b. p. 157°/15 mm., $n_D^{18°}$ 1·4843, $[\alpha]_D^{18°}$ + 37·1 (*c*, 1·40 in chloroform) (Found : C, 66·0; H, 8·7. $C_{14}H_{22}O_4$ requires C, 66·1; H, 8·66%).

The rate of polymerisation of 2 : 5-dimethallyl dianhydrosorbitol was followed viscometrically. The results below give the time of flow in seconds for the corresponding time of polymerisation in minutes (in parentheses) : 1·9 (0); 2·6 (60); 14·4 (255); 20·5 (295); 26·6 (330); 30·0 (360); 36·4 (390); 44·0 (420); 52·0 (440); 64·5 (475); 85·0 (515); 88·6 (540); 123·0 (570); 133·0 (600); 195·0 (675); 315·0 (750); 581·0 (810); 1423 (970). Further readings could not be taken in this apparatus owing to the high viscosity of the liquid. The results are shown graphically in Fig. 2.

The authors wish to express their thanks to Sir Norman Haworth, F.R.S., and Dr. J. L. Simonsen, F.R.S., for their interest, and to the Colonial Products Research Council for financial assistance.

THE A. E. HILLS LABORATORIES,
THE UNIVERSITY, EDGBASTON, BIRMINGHAM, 15. [*Received, December 24th*, 1946.]

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266. *The Preparation of* 1 : 8-*Naphthyridines from* 2 : 6-*Diaminopyridine.*

By V. PETROW, E. L. REWALD, and B. STURGEON.

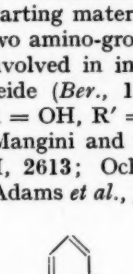
7-Amino-2-hydroxy-4-methyl-1 : 8-naphthyridine (IV; R = OH, R′ = NH_2), prepared by condensation of ethyl acetoacetate or ethyl β-aminocrotonate with 2 : 6-diaminopyridine, has been converted into 2-*chloro*-7-*acetamido*-4-*methyl*-1 : 8-*naphthyridine* (IV; R = Cl, R′ = NHAc), and hence into 2-*anilino*-, 2-p-*chloroanilino*-, 2-*piperidino*-, and 2-*phenoxy*-7-*amino*-4-*methyl*-1 : 8-*naphthyridine*.

Condensation of benzoylacetone with 2 : 6-diaminopyridine gives *7-amino-4-phenyl-2-methyl-1 : 8-naphthyridine* (V; R = NH_2), converted into *7-hydroxy-*, *7-chloro-*, and hence into *7-anilino-*, *7-piperidino-*, and *7-phenoxy-4-phenyl-2-methyl-1 : 8-naphthyridine*. (V; R = NHAc) gives the *1(N)-monoquaternary salt*.

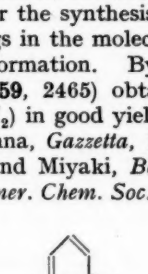
OUR interest in the naphthyridines arose from the chance observation that certain members of the series possessed valuable biological properties (see Petrow, *J.*, 1946, 200), and a comprehensive survey of the field is now in progress in these Laboratories. The present communication describes some new derivatives of 1 : 8-naphthyridine. Biological data will be reported elsewhere.

Although 2-aminopyridine would appear to form the obvious starting point for the synthesis of 1 : 8-naphthyridines, they have not hitherto been prepared from this base. Earlier claims to this effect by Reissert (*Ber.*, 1895, **28**, 119) and Räth (*Annalen*, 1931, **486**, 284; see also E.PP. 319,974, 339,932 and G.PP. 526,630, 522,272) have been conclusively disproved by Bose and Sen (*J.*, 1931, 2840), Seide and Chelinzwen (*J. Gen. Chem. Russia*, 1937, **7**, 2314), Späth and Kuffner (*Ber.*, 1938, **71**, 1657), and Petrow (*J.*, 1945, 928). It would appear that 2-aminopyridine reacts preferentially in the imino-form [partial formula (I)] to give the pyrimidine ring system such as (II) in cases of ring closure. Reactions with ethyl acetoacetate (Crippa and Scevola, *Gazzetta*, 1937, **67**, 330), ethyl benzoylacetate (Seide, *Ber.*, 1925, **58**, 352; cf. Palazzo and Tamburini, *Atti R. Accad. Lincei*, 1911, **20**, I, 37), ethyl malonate (Tschitschibabin, *Ber.*, 1924, **57**, 1169), and ethylene oxide (Knunjanz, *Ber.*, 1935, **68**, 397) have been shown to fall into this category. The recent claim of Mazza and Migliardi (*Atti R. Accad. Sci. Torino*, 1940, **75**, I, 438; see also Migliardi, *ibid.*, p. 548) that reaction of 2-aminopyridine with benzaldehyde and pyruvic acid leads to a 4-carboxy-2-phenyl-1 : 8-naphthyridine cannot be accepted. There seems little doubt that their product should be correctly formulated as the *pyrimidine* derivative (II). Räth (*Ber.*, 1925, **58**, 347; cf. Tschitschibabin, *ibid.*, p. 1704) has described the formation of a " 1 : 2-dihydro-1 : 8-naphthyridine " in low yield from the products of reaction of 2-amino-3-methylpyridine with bromoacetal at 250°. This claim, too, must be accepted with caution, as it seems unreasonable to assume the stability of a 1 : 2-dihydro-structure under the conditions of the experiment. In our view, this reaction leads to the 8-methylpyrimidazole (III). The facile formation of ring systems of this type has been demonstrated by Schmidt and Bangler (*Ber.*, 1926, **59**, 1360), Tschitschibabin (*loc. cit.*), and Allen *et al.* (*J. Amer. Chem. Soc.*, 1944, **66**, 1805). 2-Aminopyridine behaves as a cyclic amidine in these reactions, and on electro-chemical grounds alone its conversion into a 1 : 8-naphthyridine appears highly improbable.

2 : 6-Diaminopyridine, in striking contrast to 2-aminopyridine, forms the most accessible starting material for the synthesis of 1 : 8-naphthyridines, owing probably to the presence of two amino-groupings in the molecule either of which can take part in the prototropic change involved in imine-formation. By direct condensation of the base with ethyl acetoacetate, Seide (*Ber.*, 1926, **59**, 2465) obtained 7-amino-2-hydroxy-4-methyl-1 : 8-naphthyridine (IV; R = OH, R′ = NH_2) in good yield. The reaction has been extended to ethyl benzoylacetate (Mangini and Colonna, *Gazzetta*, 1942, **72**, 183), acetylacetone (Mangini, *Chem. Zentr.*, 1940, II, 2613; Ochiai and Miyaki, *Ber.*, 1941, **74**, 1115), and ethoxymethylene diethylmalonate (Adams *et al.*, *J. Amer. Chem. Soc.*, 1946, **68**, 1317).



(I.)



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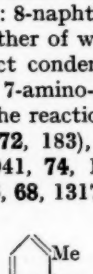

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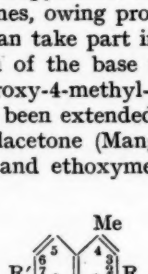
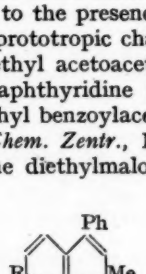


(IV.)



(V.)

We now find that 7-amino-2-hydroxy-4-methyl-1 : 8-naphthyridine (IV; R = OH, R′ = NH_2) (Seide, *loc. cit.*) passes smoothly under the action of acetic anhydride into 7-acetamido-2-hydroxy-4-methyl-1 : 8-naphthyridine (Mangini and Colonna, *loc. cit.*). The acetamido-grouping in this compound proved stable to phosphorus oxychloride, giving *2-chloro-7-acetamido-4-methyl-1 : 8-naphthyridine* (IV; R = Cl, R′ = NHAc), occasionally mixed with some *2-chloro-7-amino-4-methyl-1 : 8-naphthyridine*. Treatment of (IV; R = Cl, R′ = NHAc) with phenol at 180° gave *7-acetamido-2-phenoxy-4-methyl-1 : 8-naphthyridine*, hydrolysed to the corresponding *amino*-derivative. *7-Amino-2-anilino-*, *7-amino-2-p-chloroanilino-*, and *7-amino-2-piperidino-4-methyl-1 : 8-naphthyridine* were similarly prepared.

Condensation of 2 : 6-diaminopyridine with benzoylacetone in the presence of zinc chloride

gave 7-*amino*-4-*phenyl*-2-*methyl*-1 : 8-*naphthyridine* (V; R = NH_2), characterised by preparation of the *picrate*. The derived *acetamido*-compound (V; R = NHAc) was converted *via* the methosulphate into 7-*acetamido*-4-*phenyl*-2-*methyl*-1 : 8-*naphthyridine*-1-*methiodide*, and hence into the corresponding *methochloride*. The constitution assigned to the monomethiodide followed from the formation of a highly coloured dye on heating the compound with *p*-dimethylaminobenzaldehyde in alcoholic solution containing a trace of piperidine. This colour change is almost certainly due to the formation of the corresponding 2-*p*-dimethylaminostyryl derivative, but attempts to isolate it in a state of analytical purity were unsuccessful. Treatment of (V; R = NH_2) with nitrous acid gave 7-*hydroxy*-4-*phenyl*-2-*methyl*-1 : 8-*naphthyridine* (V; R = OH), from which 7-*chloro*-, and hence 7-*phenoxy*-, 7-*anilino*-, and 7-*piperidino*-4-*phenyl*-2-*methyl*-1 : 8-*naphthyridine* were readily prepared. Attempts to condense (V; R = NH_2) with *p*-acetamidobenzenesulphonyl chloride were unsuccessful.

We have *inter alia* examined the condensation of ethyl β-aminocrotonate with 2 : 6-diaminopyridine in the hope of obtaining the isomeric 7-amino-4-hydroxy-2-methyl-1 : 8-naphthyridine, but the only product isolated as (IV; R = OH, R′ = NH_2) in somewhat better yield. The corresponding nitrile, β-aminocrotononitrile, it may be added, reacts with arylamines with exceptional facility to give the β-aryliminobutyronitriles by loss of the elements of ammonia (Meyer, *J. pr. Chem.*, 1908, **78**, 499). Its behaviour with the aminopyridines will form the subject of a later communication.

Experimental.

(M. p.s are corrected. Microanalyses are by Drs. Weiler and Strauss, Oxford.)

2-*Chloro*-7-*acetamido*-4-*methyl*-1 : 8-*naphthyridine* (IV; R = Cl, R′ = NHAc).—7-Acetamido-2-hydroxy-4-methyl-1 : 8-naphthyridine was prepared by heating finely powdered (IV; R = OH, R′ = NH_2) (Seide, *Ber.*, 1926, **59**, 2465) (2 g.) with acetic anhydride (30 ml.) under reflux for 30 mins. The heavy yellow solid changed to a flocculent white suspension. When cold, the product was collected and recrystallised from a large volume of glacial acetic acid (charcoal), giving white crystals, m. p. >310° (Found: C, 60·8; H, 5·2; N, 19·0. Calc. for $C_{11}H_{11}O_2N_3$ C, 60·8; H, 5·1; N, 19·3%). Yield 2·2 g. (89%) (Mangini and Colonna, *loc. cit.*, give m. p. <285°). The acetamido-compound (10 g.) was heated with phosphorus oxychloride (100 ml.) for 30 minutes under reflux. The product was decomposed with ice-water and made alkaline with sodium hydroxide, and the precipitated solids were recrystallised from spirit. 2-*Chloro*-7-*acetamido*-4-*methyl*-1 : 8-*naphthyridine* formed felted white needles (7·5 g.; 69%), m. p. 240° (Found: C, 55·9; H, 3·8; N, 17·8; Cl, 15·6. $C_{11}H_{10}ON_3Cl$ requires C, 56·1; H, 4·2; N, 17·8; Cl, 15·1%).

If the temperature rose somewhat during the decomposition of the phosphorus oxychloride reaction mixture, 2-*chloro*-7-*amino*-4-*methyl*-1 : 8-*naphthyridine*, white needles, m. p. 258—259°, from alcohol (Found: Cl, 21·3. $C_9H_8N_3Cl$ requires Cl, 21·7%), was also obtained, readily separated from the acetamido-compound by fractionation from alcohol in which it was less soluble. On acetylation it gave the acetamido-derivative, m. p. 240° (above).

7-*Acetamido*-2-*phenoxy*-4-*methyl*-1 : 8-*naphthyridine*.—2-Chloro-7-acetamido-4-methyl-1 : 8-naphthyridine (1 g.) was heated with phenol (3 g.) at 180° for 1 hour. The cooled melt was treated with excess of sodium hydroxide solution, and the insoluble fraction collected and heated with acetic anhydride on the water-bath. 7-*Acetamido*-2-*phenoxy*-4-*methyl*-1 : 8-*naphthyridine*, separated on cooling as long needles from aqueous alcohol, m. p. 205° (Found: C, 69·3; H, 5·2; N, 14·1. $C_{17}H_{15}O_2N_3$ requires C, 69·6; H, 5·1; N, 14·3%). Hydrolysis with alcoholic hydrochloric acid gave 7-*amino*-2-*phenoxy*-4-*methyl*-1 : 8-*naphthyridine*, needles from benzene, m. p. 216—217° (Found: C, 71·6; H, 5·3; N, 16·7. $C_{15}H_{13}ON_3$ requires C, 71·8; H, 5·2; N, 16·7%).

7-*Amino*-2-*anilino*-4-*methyl*-1 : 8-*naphthyridine* (IV; R = NHPh, R′ = NH_2).—2-Chloro-7-acetamido-4-methyl-1 : 8-naphthyridine (4 g.) was heated with aniline (10 ml.) under reflux for 3 hours. Excess of aniline was removed in steam, and the solids were collected and heated under reflux with 2N-hydrochloric acid for 1 hour. The mixture was made alkaline with sodium hydroxide and the product purified from spirit. 7-*Amino*-2-*anilino*-4-*methyl*-1 : 8-*naphthyridine* formed yellow crystals, m. p. 269—270° (Found: C, 71·6; H, 5·4; N, 23·0. $C_{15}H_{14}N_4$ requires C, 72·0; H, 5·6; N, 22·4%).

7-*Amino*-2-p-*chloroanilino*-4-*methyl*-1 : 8-*naphthyridine*.—2-Chloro-7-acetamido-4-methyl-1 : 8-naphthyridine (2·5 g.) and *p*-chloroaniline (2·5 g.) were heated under reflux in nitrobenzene (25 ml.). Vigorous reaction occurred in a few minutes and the mixture set to a semi-solid. Heating at 200° was continued for one hour. The yellow-brown solids were collected and crystallised from alcohol–light petroleum. 7-*Amino*-2-p-*chloroanilino*-4-*methyl*-1 : 8-*naphthyridine* formed ivory needles (1 g.; 33%), m. p. 224—225° (Found: C, 63·1; H, 4·9; N, 19·5; Cl, 12·5. $C_{15}H_{13}N_4Cl$ requires C, 63·3; H, 4·6; N, 19·7; Cl, 12·5%). The *hydrochloride* formed yellow needles from alcohol–light petroleum, m. p. >300° (Found: Cl, 22·8. $C_{15}H_{14}N_4Cl_2$ requires Cl, 22·9%).

7-*Amino*-2-*piperidino*-4-*methyl*-1 : 8-*naphthyridine*.—(IV; R = Cl, R′ = NHAc) (1 g.) was heated with piperidine (5 ml.) at 180° for 8 hours in a sealed tube. Excess of piperidine was removed on the water-bath. The crystalline product, after hydrolysis with concentrated hydrochloric acid (10 ml.) and alcohol (25 ml.) for 1 hour, followed by basification with sodium hydroxide, gave 7-*amino*-2-*piperidino*-4-*methyl*-1 : 8-*naphthyridine*, ivory crystals from light petroleum, m. p. 221·5—222·5° (Found: C, 69·0; H, 7·2; N, 22·7. $C_{14}H_{18}N_4$ requires C, 69·4; H, 7·4; N, 23·1%).

7-*Amino*-4-*phenyl*-2-*methyl*-1 : 8-*naphthyridine* (V; R = NH_2).—2 : 6-Diaminopyridine (20 g.), benzoylacetone (30 g.), and powdered anhydrous zinc chloride (12 g.) were heated in an oil-bath. Reaction

commenced at 135°, after which the temperature was slowly raised to 175° over 3½ hours. Solution in alcohol (200 ml.) followed by gradual precipitation with water (300 ml.) gave a granular product, further purified by solution in 2N-hydrochloric acid (charcoal) and precipitation with sodium hydroxide. For purification, the crude naphthyridine (8 g.) and acetic anhydride (80 ml.) were heated under reflux for 30 minutes. *7-Acetamido-4-phenyl-2-methyl-1 : 8-naphthyridine*, needles from benzene (30%), m. p. 207—208° (Found : C, 73·4; H, 5·4; N, 15·0. $C_{17}H_{15}ON_3$ requires C, 73·6; H, 5·4; N, 15·2%), separated on cooling. Hydrolysis with boiling 15% hydrochloric acid for 30 minutes gave *7-amino-4-phenyl-2-methyl-1 : 8-naphthyridine*, pale yellow octahedra from nitrobenzene, m. p. 247·5—248·5° (Found : C, 76·4; H, 5·6; N, 18·1. $C_{15}H_{13}N_3$ requires C, 76·6; H, 5·5; N, 17·9%), characterised as the *picrate*, fine yellow needles from a large volume of alcohol, m. p. 284° (decomp.) (Found : N, 18·1. $C_{15}H_{13}N_3,C_6H_3O_7N_3$ requires N, 18·1%).

7-Acetamido-4-phenyl-2-methyl-1 : 8-naphthyridine-1-(N)-methiodide, prepared *via* the methosulphate, formed silky yellow needles (75%) from alcohol, m. p. 244—245° (Found : I, 31·2. $C_{18}H_{18}ON_3I$ requires I, 30·4%). The *methochloride* formed pale green platelets from alcohol–ether, m. p. 235—236° (Found : Cl, 11·1. $C_{18}H_{18}ON_3Cl$ requires Cl, 10·8%).

7-Hydroxy-4-phenyl-2-methyl-1 : 8-naphthyridine (V; R = OH).—The amino-compound (V; R = NH_2) (10 g.) in water (250 ml.) and concentrated hydrochloric acid (5 ml.), mechanically stirred at 0°, was treated simultaneously during 30 minutes with sodium nitrite (4·5 g. in 20 ml. water) and hydrochloric acid (10 ml. in 30 ml. water). After 2 hours the mixture was heated on the water-bath until evolution of nitrogen had ceased. The product was precipitated with ammonium hydroxide (*d* 0·88), giving *7-hydroxy-4-phenyl-2-methyl-1 : 8-naphthyridine*, needles from alcohol, m. p. 252—253° (Found : C, 76·3; H, 5·2; N, 11·6. $C_{15}H_{12}ON_2$ requires C, 76·2; H, 5·1; N, 11·9%). The compound dissolves in sodium hydroxide solution.

7-Chloro-4-phenyl-2-methyl-1 : 8-naphthyridine (V; R = Cl).—The hydroxy-compound (V; R = OH) (2 g.) and phosphorus oxychloride (15 ml.) were heated under reflux at 140—150° for 30 minutes. The product, isolated in the usual way, gave *7-chloro-4-phenyl-2-methyl-1 : 8-naphthyridine* (70%), felted needles from aqueous methanol (charcoal), m. p. 161° (Found : Cl, 14·4. $C_{15}H_{11}N_2Cl$ requires Cl, 14·0%).

7-Phenoxy-4-phenyl-2-methyl-1 : 8-naphthyridine separated from benzene–light petroleum in needles (80%), m. p. 156—157·5° (Found : C, 80·6; H, 5·3; N, 8·9. $C_{21}H_{16}ON_2$ requires C, 80·7; H, 5·2; N, 8·9%).

7-Anilino-4-phenyl-2-methyl-1 : 8-naphthyridine formed pale yellow needles from a large volume of alcohol, m. p. 286—287° (Found : C, 80·4; H, 5·6; N, 13·3. $C_{21}H_{17}N_3$ requires C, 81·0; H, 5·5; N, 13·5%).

7-Piperidino-4-phenyl-2-methyl-1 : 8-naphthyridine, isolated as the *picrate*, long yellow needles from alcohol, m. p. 220—221° (decomp. at 238°) (Found : N, 15·7. $C_{20}H_{21}N_3,C_6H_3O_7N_3$ requires N, 15·8%), formed pale yellow plates from benzene–light petroleum, m. p. 131—132° (Found : C, 79·0; H, 7·0; N, 14·0. $C_{20}H_{21}N_3$ requires C, 79·2; H, 6·9; N, 13·9%).

7-Amino-2-hydroxy-4-methyl-1 : 8-naphthyridine (IV; R = OH, R′ = NH_2).—2 : 6-Diaminopyridine (5 g.) and ethyl β-aminocrotonate (6 g.) were heated at 180—200° for 2 hours, after which the temperature was raised to 220° during 45 minutes, the mixture then solidifying. The grey-green mass was extracted with alcohol, giving (IV; R = OH, R′ = NH_2), m. p. >360°, identified by acetylation and chlorination to (IV; R = Cl, R′ = NHAc), m. p. 240°, alone or in admixture with an authentic specimen (above), further converted into (IV; R = OPh, R′ = NH_2), m. p. 214—215°, alone or in admixture with an authentic specimen.

The authors thank the Therapeutic Research Corporation of Great Britain Limited for grants and for certain facilities.

QUEEN MARY COLLEGE (UNIVERSITY OF LONDON), E.1. [*Received, December 31st*, 1946.]

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267. *Contributions to the Chemistry of Phenanthridine. Part I. The Conversion of 9-(3′-Pyridyl)phenanthridines into their Quaternary Salts and the Preparation of Some Derivatives of Potential Biological Interest.*

By V. PETROW and W. R. WRAGG.

9-(3′-*Pyridyl*)- (II; R = R′ = H), 3-*nitro*-9-(3′-*pyridyl*)- (II; R = NO_2, R′ = H), and 7-*nitro*-9-(3′-*pyridyl*)-*phenanthridine* (II; R = H, R′ = NO_2) have been obtained from the appropriate 2-*nicotinamidodiphenyls*. Conversion of the first two compounds into their mono-quaternary *salts* led to the formation of the py-N-*methylmethosulphates*, the constitution of which followed from their oxidation to the corresponding N-*methylpyridones*.* As expected, the *monomethiodide* derived from 9-(6′-*keto*-1′-*methyl*-1′ : 6′-*dihydro*-3′-*pyridyl*)*phenanthridine* (IV; R = H) possessed the anticipated properties of a phenanthridyl-*N*-methiodide.

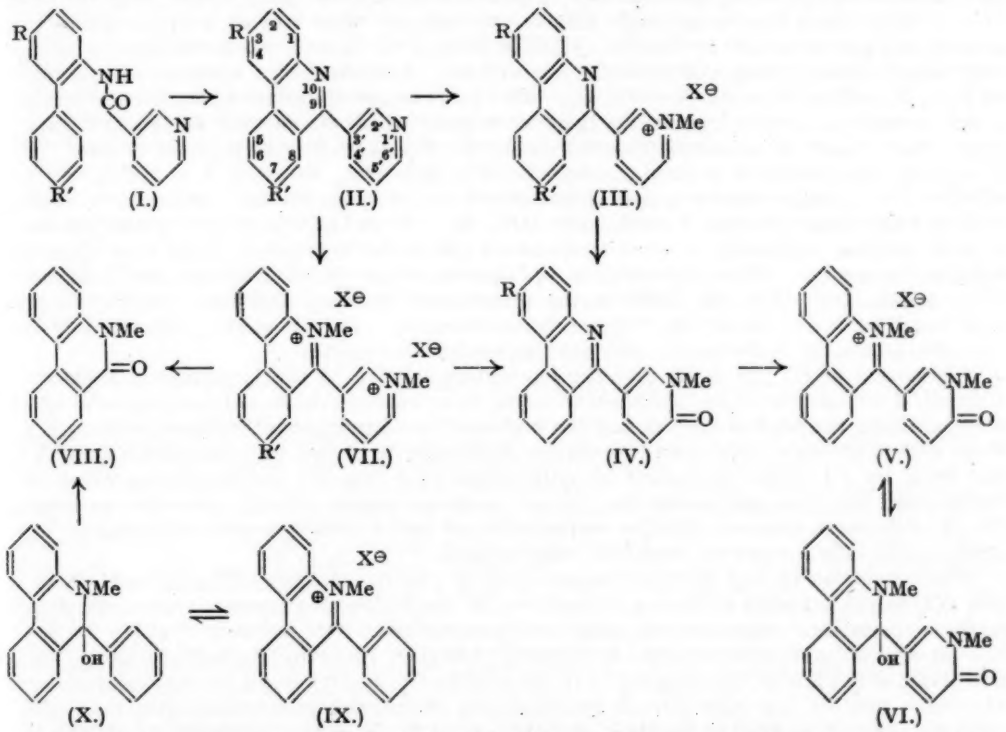
Treatment of 9-(3′-*pyridyl*)*phenanthridine* 1′ : 10-*dimethiodide* (VII; R′ = H, X = I) with excess of aqueous sodium hydroxide followed by potassium ferricyanide at room temperature gave (IV; R = H). Reaction with boiling alcoholic sodium hydroxide, however, resulted in

* These *N*-methylpyridones may clearly be either 2′- or 6′-pyridones. The question is irrelevant to the present investigation and the orientation of a 6′-pyridone has been *assumed* throughout.

loss of the pyridyl-1′-methiodide grouping and the production of 10-methyl-9-phenanthridone (VIII), also obtained by the action of alcoholic alkaline ferricyanide on *9-phenylphenanthridine 10-methylmethosulphate* (IX; X = $MeSO_4$).

Reduction of the two nitro-9-(3′-pyridyl)phenanthridines (II; R = NO_2, R′ = H, and R = H, R′ = NO_2) and their py-N-*methylmethosulphates* gave the corresponding *amino*-compounds.

FOLLOWING recent work on the relationship between structure and biological activity in the phenanthridine series (Petrow, *J.*, 1945, 18; Walls, *ibid.*, p. 294), we have now synthesised some 9-(3′-pyridyl)phenanthridines. We required these for examination as trypanocides, and also, from their formal analogy to the pyridyl quinolines of Coates, Cook, Heilbron, Hey, Lambert, and Lewis (*J.*, 1943, 401), for study as spasmolytics.



Condensation of nicotinyl chloride hydrochloride with 2-aminodiphenyl in boiling chlorobenzene solution led to the formation of *2-nicotinamidodiphenyl* (I; R = R′ = H) in 78% yield. *5-Nitro-* (I; R = NO_2, R′ = H), and *4′-nitro-2-nicotinamidodiphenyl* (I; R = H, R′ = NO_2) were similarly prepared from the appropriate diphenyls. Ring closure of these compounds failed to take place on heating them with phosphorus oxychloride alone, but was readily accomplished by using phosphorus oxychloride in nitrobenzene solution (B.P. 520, 273; cf. Walls, *loc. cit.*) giving 9-(3′-*pyridyl*)- (II; R = R′ = H) and *3-nitro-9-(3′-pyridyl)-phenanthridine* (II; R = NO_2, R′ = H) in excellent yields. When 4′-nitro-2-nicotinamidodiphenyl (I; R = H, R′ = NO_2) was employed, however, ring closure appeared incomplete after 24 hours' heating, and the yield of *7-nitro-9-(3′-pyridyl)phenanthridine* (II; R = H, R′ = NO_2) was only 37%. This result is a further illustration of the polar influence of the 4′-nitro-grouping in depressing the mobility of the 2′-hydrogen atom involved in ring closure (cf. Morgan and Walls, *J.*, 1938, 390; Petrow, *loc. cit.*).

Conversion of (II; R = R′ = H) into the mono-quaternary salt may clearly involve either the pyridyl or phenanthridyl basic centres. We have decided in favour of the former alternative on the following evidence. Reaction of 9-phenylphenanthridine, a compound structurally related to (II; R = R′ = H) but possessing only the phenanthridyl basic centre, with methyl sulphate, led to the formation of *9-phenylphenanthridine 10-methylmethosulphate* (IX; X = $MeSO_4$), converted by one molar equivalent of sodium hydroxide into the *pseudo-base* (X). Although this reaction may also yield the methohydroxide, it has been assumed by earlier

workers that the product obtained is actually the pseudo-base where experimental evidence favours such a conclusion; pseudo-bases differ from the corresponding quaternary hydroxides in that they are relatively insoluble in water and soluble in non-hydroxylic solvents (*e.g.*, light petroleum). The pseudo-base reverted on treatment with 1·15 molar equivalents of hydrochloric acid to the quaternary salt, converted by potassium iodide into the normal *methiodide*. These model transformations serve to characterise systems such as (IX). The reactions of the monoquaternary salts obtained from (II) with, in the first place, alkali, and secondly potassium ferricyanide–sodium hydroxide, however, followed a different pattern which could be interpreted only by assuming that it was the pyridyl nitrogen which was involved in salt formation. Thus both 9-(3′-*pyridyl*)*phenanthridine* 1′-*methiodide* (III; R = R′ = H, X = I) and 3-*nitro*-9-(3′-*pyridyl*)*phenanthridine* 1′-*methylmethosulphate* (III; R = NO_2, R′ = H, X = $MeSO_4$) failed to give sparingly soluble pseudo-bases when treated with one molar proportion of aqueous sodium hydroxide. (III; R = R′ = H; X = I) was unchanged by heating with excess dilute sodium hydroxide for one minute. Treatment of a warm aqueous solution of (III; R = NO_2, R′ = H, X = $MeSO_4$) with a large excess of sodium hydroxide precipitated a red amorphous material, probably the pseudo-base, which on vacuum sublimation gave a very small yield of 3-*nitro*-9-(6′-*keto*-1′-*methyl*-1′ : 6′-*dihydro*-3′-*pyridyl*)*phenanthridine* (IV; R = NO_2), also obtained in good yield from (III; R = NO_2, R′ = H, X = $MeSO_4$) by hot alkaline ferricyanide oxidation, and characterised as its *hydrochloride*. Attempts to oxidise 9-(3′-pyridyl)phenanthridine 1′-methiodide (III; R = R′ = H, X = I) with potassium ferricyanide–sodium hydroxide at room temperature led to the separation of the very sparingly soluble *ferricyanide*. When the reaction was carried out at 80° (cf. Diesbach and Aeschbach, *Helv. Chim. Acta*, 1945, **28**, 1392) in the presence of benzene, oxidation occurred to give 9-(6′-*keto*-1′-*methyl*-1′ : 6′-*dihydro*-3′-*pyridyl*)*phenanthridine* (IV; R = H), characterised by conversion into the *hydrochloride* and the *thiopyridone* derivative.

Conversion of (IV; R = H) into the quaternary salt led to the formation of 9-(6′-*keto*-1′-*methyl*-1′ : 6′-*dihydro*-3′-*pyridyl*)*phenanthridine* 10-*methiodide* (V; X = I), a compound which now exhibited the typical reactions of the 9-phenyl-10-methylphenanthridinium system (IX). Thus with 1·05 molar equivalent of sodium hydroxide it passed into the *pseudo-base* (VI), converted by 1·1 molar equivalent of hydrochloric acid into the methochloride, which was transformed into the methiodide (V; X = I) with potassium iodide. Attempts to oxidise (V; X = I) with aqueous alkaline ferricyanide at 80° in the presence of benzene were unsuccessful, only the pseudo-base (VI) being isolated.

The conversion of 9-(3′-*pyridyl*)*phenanthridine* 1′ : 10-*dimethiodide* (VII; R′ = H, X = I) into (VI) would complete the series of reactions (II) to (VI) by two separate routes and supply further experimental evidence confirming these formulations. On treatment of (VII; R′ = H, X = I) with 50% alcoholic alkaline ferricyanide, however, 10-methyl-9-phenanthridone (VIII) was obtained in place of the expected (VI), the quaternary pyridyl group having been removed. The same product was also formed by employing 9-phenylphenanthridine-10-methylmethosulphate (IX; X = $MeSO_4$) in place of (VII; R′ = H, X = I). Attempts to oxidise (V; X = I) with 50% alcoholic alkaline ferricyanide, however, gave (VI) and not the phenanthridone (VIII). Further work showed that (VII; R′ = H, X = I) could be converted into (VIII) by simply refluxing it with 50% alcoholic dilute sodium hydroxide. Treatment of (VII; R′ = H, X = I) dissolved in a large excess of cold 2N-sodium hydroxide with potassium ferricyanide in very dilute solution, resulted in the loss of the quaternary group attached to the phenanthridyl nitrogen, the product isolated being (IV; R = H). Pictet and Patry (*Ber.*, 1893, **26**, 1966) have described the alkaline ferricyanide oxidation of phenanthridine 10-methiodide to 10-methyl-9-phenanthridone (VIII), and have also shown (*Ber.*, 1902, **35**, 2534) that steam distillation of phenanthridine 10-methohydroxide yields 10-methyl-9 : 10-dihydrophenanthridine and (VIII). Morgan and Walls (*J.*, 1938, 391) have obtained (VIII) by heating 9-dimethylaminophenanthridine 10-methiodide with water. The formation of (VIII) from (VII; R′ = H; X = I) and (IX; X = I) represents an extension of these observations, in that the elimination of a 9-aryl substituent is involved. This may take place by an oxidation of the tertiary C_9 alcohol (*e.g.*, X), or in the case of (VII; R′ = H; X = I) which yields (VIII) by simple treatment with alkali, by direct transference of hydrogen from the C_9 hydroxyl group to the quaternary pyridyl group.

3- (III; R = NH_2, R′ = H, X = Cl) and 7-*Amino*-9-(3′-*pyridyl*)*phenanthridine* 1′-*methochloride* (III; R = H, R′ = NH_2, X = Cl) were best prepared from the corresponding *methiodides*. These were obtained by reducing the appropriate nitro-9-(3′-pyridyl)phenanthridine 1′-monomethylmethosulphate with reduced iron in acidified aqueous solution followed

by treatment of the reduction liquor with potassium iodide. Catalytic methods led to nuclear reduction.

3- (II; R = NH_2, R′ = H) and 7-*Amino*-9-(3′-*pyridyl*)*phenanthridine* (II; R = H, R′ = NH_2), obtained from the corresponding nitro-compounds by reduction with stannous chloride, were characterised by preparation of the *acetyl* derivatives. These gelatinous compounds were obtained crystalline only after sublimation in a high vacuum. 7-Amino-9-(3′-pyridyl)phenanthridine (II; R = H, R′ = NH_2) was also obtained in 31% yield by catalytic reduction of the corresponding nitro-compound in glacial acetic acid with Adams's platinum oxide catalyst. When 2N-hydrochloric acid was substituted as solvent, however, simultaneous nuclear reduction invariably took place. As expected, attempts at the further reduction of the 7-amino-compound (II; R = H, R′ = NH_2) in methanol or glacial acetic acid were unsuccessful, whereas nuclear reduction again occurred in 2N-hydrochloric acid.

The spasmolytic activities of (II; R = R′ = H), (II; R = NH_2, R′ = H), and (II; R = H, R′ = NH_2) have been very kindly determined for us by Mr. R. Thorp (Wellcome Physiological Research Laboratories, Beckenham, Kent). The $L.D._{50}$ of all three compounds, determined by intravenous injection in mice, was approximately 0·06 mg./g. Upon the isolated rabbit intestinal segment, a dilution of 1 : 100,000 of all three substances was about as effective as 1 : 50,000,000 of " trasentin " in relaxing the spasm caused by a 1 : 3,000,000 dilution of carbinoyl choline. Their spasmolytic activity was thus not of a high order.

The results of trypanocidal tests on (III; R = NH_2, R′ = H, X = Cl) and (III; R = H, R′ = NH_2, X = Cl) have already been reported (Wien, *Brit. J. Pharmacol.*, 1946, **1**, 65). At the time these were carried out we had not reached a decision as to the structure of the mono-quaternary salts, to which Dr. Wien provisionally ascribed the phenanthridyl *N*-methochloride formulation.

Experimental.

Semimicro-analyses are by Mr. S. Bance, B.Sc., A.R.I.C., Research Laboratories, May and Baker, Ltd. Melting points are corrected.

2-*Nicotinamidodiphenyl* (I; R = R′ = H).—Nicotinic acid (90 g.) was heated under reflux for 1 hour with thionyl chloride (250 c.c.), the mixture taken to dryness under reduced pressure on the water-bath, and the residue dissolved during 20 minutes in boiling chlorobenzene (1 l.). On addition of 2-aminodiphenyl (120 g.) in warm chlorobenzene (200 c.c.) a vigorous reaction occurred with evolution of hydrogen chloride and separation of a red oil which solidified. The solid product was collected, washed with ether, and crystallised from solution in methanol (1 l.) by addition of excess of aqueous ammonia. 2-*Nicotinamidodiphenyl* formed colourless octahedra from aqueous methanol (157 g.; 78%); m. p. 173—174° (Found: C, 78·8; H, 5·1; N, 10·4. $C_{18}H_{14}ON_2$ requires C, 78·8; H, 5·1; N, 10·2%).

5-*Nitro*-2-*nicotinamidodiphenyl* (I; R = NO_2, R′ = H).—Nicotinyl chloride hydrochloride (from 5 g. acid) dissolved in boiling chlorobenzene (35 c.c.), was treated with 5-nitro-2-aminodiphenyl (7 g.) for 5 minutes under reflux. After addition of pyridine (10 c.c.) and heating for 5 minutes, the mixture was cooled and the product precipitated with light petroleum (50 c.c.). The free base was obtained by crystallisation from alcohol (150 c.c.)–2N-ammonia (excess). 5-*Nitro*-2-*nicotinamidodiphenyl* formed long cream prisms from aqueous alcohol (8·6 g.; 83%); m. p. 160—161° (Found: C, 67·9; H, 4·2; N, 13·3. $C_{18}H_{13}O_3N_3$ requires C, 67·7; H, 4·0; N, 13·2%).

4′-*Nitro*-2-*nicotinamidodiphenyl* (I; R = H, R′ = NO_2).—Nicotinyl chloride hydrochloride (from 25 g. acid) in boiling chlorobenzene (200 c.c.) was treated with 4′-nitro-2-aminodiphenyl (35 g.) for 30 minutes under reflux. After addition of pyridine (30 c.c.) and a further 15 minutes heating, the product was precipitated with an equal volume of light petroleum (b. p. 100—120°). By solution in pyridine (400 c.c.; charcoal) and precipitation with excess of 2N-ammonia, 4′-*nitro*-2-*nicotinamidodiphenyl* was obtained, separating from pyridine–light petroleum (1 : 1) in small cream irregular prisms (40 g.; 77%); m. p. 226—227° (Found: C, 67·7; H, 4·0; N, 13·4. $C_{18}H_{13}O_3N_3$ requires C, 67·7; H, 4·0; N, 13·2%). Attempted preparations of this compound in pyridine at 100° instead of in boiling chlorobenzene yielded a product which could not readily be purified.

9-(3′-*Pyridyl*)*phenanthridine* (II; R = R′ = H).—Phosphorus oxychloride (30 c.c.), 2-nicotinamidodiphenyl (20 g.), and nitrobenzene (200 c.c.) were heated under reflux for 20 hours. The mixture was basified with concentrated ammonia at 0° and the nitrobenzene removed in steam. The solids were collected and dissolved in concentrated hydrochloric acid (200 c.c.; charcoal), and the base was precipitated with ammonia at 0°. 9-(3′-*Pyridyl*)*phenanthridine* formed colourless needles from light petroleum (b. p. 80—100°) (13·5 g.; 72%); m. p. 125—127° (Found: C, 84·0; H, 4·7; N, 11·2. $C_{18}H_{12}N_2$ requires C, 84·4; H, 4·7; N, 10·9%). With methyl sulphate (0·95 mol.) in boiling benzene for ½ hour it gave the 1′-methylmethosulphate, converted in aqueous solution into the 1′-*methiodide* (III; R = R′ = H, X = I), yellow elongated plates from methanol of indefinite m. p. 259—269° (Found: N, 7·2; I, 32·0. $C_{18}H_{12}N_2,CH_3I$ requires N, 7·0; I, 32·0%). The 1′-*methoferricyanide*, obtained by treating a warm aqueous solution of the 1′-methylmethosulphate with potassium ferricyanide, crystallised from aqueous methanol in irregular yellow plates, decomposing above 180° [Found: N, 16·2; Fe, 5·4. $(C_{18}H_{15}N_2)_3,Fe(CN)_6$ requires N, 16·4; Fe, 5·4%]. Reaction of (II; R = R = H; 5·1 g.) with methyl sulphate (7·6 c.c.; 4 mols.) in dry nitrobenzene (400 c.c.) at 170—180° for 30 minutes gave the 1′ : 10-dimethyldimethosulphate. Removal of nitrobenzene in steam, followed by addition of potassium iodide (20 g.) to the residual aqueous liquor (250 c.c.), gave the corresponding 1′ : 10-*dimethiodide* (VII; R′ = H, X = I). This salt formed golden irregular plates (8·8 g.; 82%)

from water; m. p. 237—242° with effervescence (preheated bath at 200°), resolidifying and melting again at 270—275° (Found: N, 5·2; I, 46·8. $C_{18}H_{12}N_2,2CH_3I$ requires N, 5·2; I, 47·0%).

3-*Nitro*-9-(3′-*pyridyl*)*phenanthridine* (II; R = NO_2, R′ = H).—Phosphorus oxychloride (200 c.c.), 5-nitro-2-nicotinamidodiphenyl (90 g.), and nitrobenzene (1·6 l.) were refluxed for 20 hours. The brown product which separated on cooling was boiled with pyridine (1 l.)–2N-ammonia (600 c.c.). 3-*Nitro*-9-(3′-*pyridyl*)*phenanthridine* separated from pyridine in faintly yellow felted needles (80 g.; 94%); m. p. 250—252° (Found: C, 71·9; H, 3·8; N, 14·0. $C_{18}H_{11}O_2N_3$ requires C, 71·7; H, 3·7; N, 13·9%). The base (15 g.) was treated in nitrobenzene (400 c.c.) with methyl sulphate (4·5 c.c.; 0·95 mol.) at 170°, followed by precipitation with ether (300 c.c.). The 1′-*methylmethosulphate* (86% yield) formed bulky colourless needles from methanol–ether; m. p. 210—212° (preheated bath) [Found N, 9·7; S, 7·5. $C_{18}H_{11}O_2N_3,(CH_3)_2SO_4$ requires N, 9·9; S, 7·5%].

7-*Nitro*-9-(3′-*pyridyl*)*phenanthridine* (II; R = H, R′ = NO_2), prepared (37% yield) in a similar manner to (II; R = NO_2; R′ = H) separated in felted buff needles from pyridine; m. p. 292—293° (Found: C, 71·8; H, 3·7; N, 14·0. $C_{18}H_{11}O_2N_3$ requires C, 71·7; H, 3·7; N, 13·9%). Reaction of (II; R = H, R′ = NO_2) in nitrobenzene at 170° with methyl sulphate (0·9 mol.) gave the 1′-*methylmethosulphate* (III; R = H, R′ = NO_2, X = $MeSO_4$), small irregular plates from methanol–ether (78% yield); m. p. 251—253° (with previous softening) [Found: N, 9·8; S, 7·6. $C_{18}H_{11}O_2N_3,(CH_3)_2SO_4$ requires N, 9·9; S, 7·5%]. When the methyl sulphate was increased to 3 mols. the 1′ : 10-*dimethyldimethosulphate* (VII; R′ = NO_2, X = $MeSO_4$) was obtained, small cream plates from methanol–ether; m. p. 256—258° (with previous softening) [Found: N, 7·5; S, 11·7. $C_{18}H_{11}O_2N_3,2(CH_3)_2SO_4$ requires N, 7·6; S, 11·6%]. The 1′-*methopicrate* formed bright yellow irregular needles from acetone; m. p. 300—302° (Found: N, 15·4. $C_{18}H_{11}O_2N_3,C_7H_5O_7N_3$ requires N, 15·5%).

Model Experiments with Quaternary Salts of 9-*Phenylphenanthridine.*—Reaction of 9-phenylphenanthridine (Morgan and Walls, *J.*, 1931, 2451) in benzene with methyl sulphate (2 mols.) gave the 10-*methylmethosulphate* (IX; X = $MeSO_4$) which separated from alcohol–ether in colourless prisms, m. p. 222—224° [Found: N, 4·0; S, 8·4. $C_{19}H_{13}N,(CH_3)_2SO_4$ requires N, 3·7; S, 8·4%]. The 10-*methiodide* (IX; X = I) crystallised from water as well-defined bright yellow prisms which decomposed sharply at temperatures between 235 and 260°, depending on the rate of heating (Found: N, 3·7; I, 32·1. $C_{19}H_{13}N,CH_3I$ requires N, 3·6; I, 32·0%). The *pseudo-base* (X), precipitated from an aqueous solution of the 10-methylmethosulphate (IX; X = $MeSO_4$) by 1 mol. of N-sodium hydroxide, was extracted with ethyl acetate. It crystallised from light petroleum (b. p. 80—100°) in colourless prisms, m. p. 132—136° (Found: C, 83·8; H, 6·0; N, 5·0. $C_{20}H_{17}ON$ requires C, 83·6; H, 5·9; N, 4·9%). The pseudo-base (0·025 g.) dissolved in water (2 c.c.) containing N/10-hydrochloric acid (1 c.c.; 1·15 mol.), was treated with potassium iodide (0·3 g.), giving 9-phenylphenanthridine 10-methiodide (IX; X = I) identical with an authentic specimen.

9-(6′-*Keto*-1′-*methyl*-1′ : 6′-*dihydro*-3′-*pyridyl*)*phenanthridine* (IV; R = H).—The yellow suspension obtained by treating a warm solution of 9-(3′-pyridyl)phenanthridine 1′-methiodide (8 g.) in water (400 c.c.) with potassium ferricyanide (20 g. in 50 c.c. water) was made alkaline by addition of 2N-sodium hydroxide (50 c.c.) and then vigorously stirred on the steam-bath for 40 minutes. Benzene (1 l.) was added to take up the product as it was formed. The red benzene layer was separated, washed with water (50 c.c.), and concentrated to 100 c.c. under reduced pressure. Addition of light petroleum precipitated 9-(6′-*keto*-1′-*methyl*-1′ : 6′-*dihydro*-3′-*pyridyl*)*phenanthridine* (4·1 g.; 70%), small buff prisms from chloroform–acetone; m. p. 211—212° (Found: C, 79·7; H, 5·0; N, 9·8. $C_{19}H_{14}ON_2$ requires C, 79·7; H, 4·9; N, 9·8%). A 57% yield of (IV; R = H) was also obtained by adding 2N-sodium hydroxide (2 c.c.) in one portion to a solution of 9-(3′-pyridyl)phenanthridine 1′-methiodide (0·4 g.) and potassium ferricyanide (1·6 g.) in 50% ethanol (40 c.c.), and refluxing the mixture for 30 minutes. The product was isolated by removing the ethanol under reduced pressure and extracting the residual suspension with benzene. Although (IV; R = H) was largely insoluble in boiling 2N-hydrochloric acid (0·13 g. in 4 c.c.), the *hydrochloride* was obtained by diluting a solution in warm concentrated hydrochloric acid (0·3 g. in 3 c.c.) with water (25 c.c.). Fawn hydrated needles separated which decomposed evolving hydrochloric acid gas above 205° (Found: C, 66·6; H, 5·3; N, 8·3; Cl, 10·3. $C_{19}H_{14}ON_2,HCl,H_2O$ requires C, 66·9; H, 5·0; N, 8·2; Cl, 10·4%). The *thiopyridone* derivative was obtained by refluxing the pyridone (IV; R = H; 0·57 g.) in chlorobenzene (20 c.c.) with finely powdered phosphorus pentasulphide (1·4 g.) for 1 hour. The hot reaction mixture was filtered and the insoluble material triturated with 2N-sodium hydroxide (40 c.c.). The brown insoluble residue (0·3 g.) was collected. It crystallised from alcohol (15 c.c.) in fawn prisms (0·1 g.), m. p. 182—197° (Found: N, 9·4; S, 10·8. $C_{19}H_{14}N_2S$ requires N, 9·3; S, 10·6%).

3-*Nitro*-9-(6′-*keto*-1′-*methyl*-1′ : 6′-*dihydro*-3′-*pyridyl*)*phenanthridine* (IV; R = NO_2).—2N-Sodium hydroxide (20 c.c.) was added to the yellow suspension obtained when 3-nitro-9-(3′-pyridyl)phenanthridine 1′-methylmethosulphate (1 g.) in water (250 c.c.) at 60° was treated with potassium ferricyanide (3 g.). The mixture was then rapidly heated to boiling. After 15 minutes the suspension was cooled. The solid *product*, washed free from alkali, crystallised from pyridine (25 c.c.)–methanol (50 c.c.) as well-defined light brown needles (0·5 g.; 65%); m. p. 304—305° (Found: C, 68·8; H, 4·2; N, 12·8. $C_{19}H_{13}O_3N_3$ requires C, 68·9; H, 4·0; N, 12·7%). Sublimation of the red amorphous precipitate (2·2 g.) obtained by precipitating a warm aqueous solution (40 c.c.) of 3-nitro-9-(3′-pyridyl)phenanthridine 1′-methylmethosulphate (3·2 g.) with sodium hydroxide (15 c.c. of 50% w/v. solution), at 280°/0·02 mm. yielded a yellow crystalline sublimate (0·1 g.). After crystallisation from pyridine–light petroleum, (IV; R = NO_2) was obtained, m. p. 304—305°, not depressed in admixture with an authentic sample (Found: C, 68·9; H, 4·3; N, 12·6%). Although (IV; R = NO_2) was insoluble in boiling N-hydrochloric acid (0·1 g. in 4 c.c.), the *hydrochloride* was prepared by diluting a solution in hot concentrated hydrochloric acid. The salt separated in well-defined brown prisms which evolved hydrogen chloride above 140° and melted at 303—305° (Found: N, 11·2; Cl, 9·8. $C_{19}H_{13}O_3N_3,HCl$ requires N, 11·4; Cl, 9·7%). A mixed melting point of this hydrochloride and the corresponding base showed no depression.

9-(6′-*Keto*-1′-*methyl*-1′ : 6′-*dihydro*-3′-*pyridyl*)*phenanthridine* 10-*Methiodide* (V; X = I).—9-(6′-Keto-1′-methyl-1′ : 6′-dihydro-3′-pyridyl)phenanthridine (4·2 g.) was treated in xylene (150 c.c.) with

methyl sulphate (6 c.c.; 4 mols.) for 30 minutes. The gum which separated on cooling was dissolved in hot water (100 c.c.). Addition of potassium iodide (9 g.) gave the *methiodide*, golden prisms from water (2·9 g.); m. p. 240—243° (decomp.) (Found: N, 6·6; I, 29·7. $C_{19}H_{16}ON_2,CH_3I$ requires N, 6·5; I, 29·7%). The methiodide (0·4 g.) in ethanol (5 c.c.) was treated with N-sodium hydroxide (1 c.c.; 1·05 mol.). On dilution with water the *pseudo-base* (VI) was precipitated, forming irregular colourless prisms from aqueous alcohol (0·24 g.; 80%); m. p. 194—196° (Found: C, 75·3; H, 5·96; N, 8·9. $C_{30}H_{18}O_2N_2$ requires C, 75·5; H, 5·7; N, 8·8%). The pseudo-base (0·029 g.) dissolved in water (6 c.c.) containing N/10-hydrochloric acid (1 c.c.; 1·1 mol.) was treated with potassium iodide (0·3 g.), giving 9-(6′-keto-1′-methyl-1′ : 6′-dihydro-3′-pyridyl)phenanthridine 10-methiodide (V; X = I) identical with an authentic specimen.

Attempted Oxidations of 9-(3′-*Pyridyl*)*phenanthridine* 1′ : 10-*Dimethiodide* (VII; R′ = H, X = I).—(*a*) 2N-Sodium hydroxide (2 c.c.) was added to a boiling solution of 9-(3′-pyridyl)phenanthridine 1′ : 10-dimethiodide (0·54 g.) and potassium ferricyanide (1·6 g.) in 50% ethanol (40 c.c.). After 30 minutes the alcohol was removed and the insoluble precipitate crystallised from light petroleum (b. p. 80—100°); colourless needles of 10-methyl-9-phenanthridone (VIII) separated (0·12 g.; 57%); m. p. 108—110° (Pictet and Patry, *Ber.*, 1893, **26**, 1966, give m. p. 108°) (Found: N, 6·8. Calc. for $C_{14}H_{11}ON$: N, 6·7%). If the potassium ferricyanide were omitted in the above preparation the yield of (VIII) fell to 24%. When 9-phenylphenanthridine 10-methylmethosulphate was substituted for (VII; R′ = H; X = I) in the above alcoholic alkaline ferricyanide oxidation a 23% yield of (VIII) was obtained (Found: C, 80·5; H, 5·5%). The identity of this product was confirmed by a mixed melting point determination.

(*b*) Potassium ferricyanide (5·4 g.) was dissolved in a cold solution of the dimethiodide (VII; R′ = H, X = I) in 2N-sodium hydroxide (40 c.c.) diluted to 1 l. with water. After two days the collected precipitated solids were extracted with ethanol (10 c.c.). The white solid which separated from the filtered extract crystallised from benzene–light petroleum as almost white prisms (0·13 g.; 45%), m. p. 206—210°, identical with 9-(6′-keto-1′-methyl-1′ : 6′-dihydro-3′-pyridyl)phenanthridine (IV; R = H).

(*c*) A cold solution of the dimethiodide (VII; R′ = H, X = I) in water (500 c.c.) containing potassium ferricyanide (1·0 g.) was treated with N-sodium hydroxide (3 c.c.; 3 mol.). 1 C.c. of N-sodium hydroxide was added daily for 7 days by which time a stringy white precipitate had separated. This material (0·05 g.) was crystallised from aqueous alcohol and light petroleum giving 10-methyl-9-phenanthridone (VIII), m. p. 109—111°, mixed melting point with an authentic specimen 108—111°.

3-*Amino*-9-(3′-*pyridyl*)*phenanthridine* (II; R = NH_2, R′ = H).—3-Nitro-9-(3′-pyridyl)phenanthridine (4 g.) in concentrated hydrochloric acid (100 c.c.) was treated at the boiling point with stannous chloride (9 g.) in concentrated hydrochloric acid (25 c.c.), refluxing being maintained for a further 45 minutes. After being allowed to cool, the yellow stannichloride was collected and dissolved in water (40 c.c.), the base was liberated with 50% sodium hydroxide and extracted with chloroform (250 c.c.). After solution in 2N-hydrochloric acid (charcoal) and reprecipitation, it distilled at 230°/0·05 mm. and was crystallised from methanol (40 c.c.) and water (10 c.c.). 3-*Amino*-9-(3′-*pyridyl*)*phenanthridine monohydrate* formed pale yellow felted needles, m. p. 127—128° (decomp.) (Found: N, 14·7. $C_{18}H_{13}N_3,H_2O$ requires N, 14·5%). The anhydrous *base* formed light brown rectangular rods from benzene (1·2 g.; 33%); m. p. 165—166° (Found: C, 79·5; H, 4·6; N, 15·3. $C_{18}H_{13}N_3$ requires C, 79·7; H, 4·8; N, 15·5%). The *acetyl* derivative was prepared by heating the base (0·5 g.) and a little anhydrous sodium acetate in glacial acetic acid (5 c.c.) and acetic anhydride (5 c.c.) for 1½ hours. After sublimation at 260°/10 mm. it formed flat needles (0·3 g.); m. p. 253° (Found: C, 77·1; H, 4·9; N, 13·4. $C_{20}H_{15}ON_3$ requires C, 76·7; H, 4·8; N, 13·4%).

3-*Amino*-9-(3′-*pyridyl*)*phenanthridine* 1′-*Methochloride* (III; R = NH_2, R′ = H, X = Cl).—Reduced iron (5 g.) was added as rapidly as possible to a boiling aqueous solution (40 c.c.) of 3-nitro-9-(3′-pyridyl)-phenanthridine 1′-methylmethosulphate (4·27 g.), previously acidified (Congo-red) with 2N-sulphuric acid. After 30 minutes the mixture was filtered (charcoal) and treated with potassium iodide (5 g.). After 12 hours at 0° the solids were collected and crystallised from water (50 c.c.) and then from methanol. 3-*Amino*-9-(3′-*pyridyl*)*phenanthridine* 1′-*methiodide* (III; R = NH_2, R′ = H, X = I) formed light brown irregular plates of indefinite m. p. 180—240° (Found: C, 55·1; H, 4·3; N, 10·4; I, 30·8. $C_{18}H_{13}N_3,CH_3I$ requires C, 55·2; H, 3·9; N, 10·2; I, 30·8%). The *methochloride* (III; R = NH_2; R′ = H; X = Cl) formed brown rods from ethereal methanol, m. p. 256—257° (Found: N, 13·1; Cl, 11·3. $C_{18}H_{13}N_3,CH_3Cl$ requires N, 13·1; Cl, 11·1%). It gave positive primary amine tests.

7-*Amino*-9-(3′-*pyridyl*)*phenanthridine* (II; R = H, R′ = NH_2) formed a bright red stannichloride. The base separated from chlorobenzene in yellow rods (64% yield), m. p. 227—229° (Found: C, 79·5; H, 4·6; N, 15·2. $C_{18}H_{13}N_3$ requires C, 79·7; H, 4·8; N, 15·5%). The *acetyl* derivative, after sublimation at 290—300°/0·01 mm., formed felted colourless needles, m. p. 296—298° (Found: C, 76·5; H, 5·0; N, 13·4. $C_{20}H_{15}ON_3$ requires C, 76·7; H, 4·8; N, 13·4%).

7-*Amino*-9-(3′-*pyridyl*)*phenanthridine* 1′-*Methochloride* (III; R = H, R′ = NH_2, X = Cl).—The *methiodide* (III; R = H, R′ = NH_2, X = I) separated from water in light brown needles, m. p. 243—244° (decomp.) (Found: C, 55·4; H, 3·9; N, 10·3; I, 30·8. $C_{18}H_{13}N_3,CH_3I$ requires C, 55·2; H, 3·9; N, 10·2; I, 30·8%). The *methochloride* crystallised from ethereal methanol in orange plates, m. p. 265—267° (Found: N, 12·8; Cl, 11·2. $C_{18}H_{13}N_3,CH_3Cl$ requires N, 13·1; Cl, 11·1%); it gave positive tests for a primary amine.

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268. *A Re-examination of the Reported* m-*Nitration of Phenols and Phenolic Ethers.*

By C. A. Bunton, G. J. Minkoff, and R. I. Reed.

The products of mononitration of phenol and anisole have been analysed by several independent methods for the presence of *m*-isomerides. The conclusion has been reached that, contrary to the views of earlier investigators, the proportions in which *m*-isomerides are formed in these reactions are less than 0·1%.

Arnall claimed (*J.*, 1924, **125**, 911) that 2·1—3·3% of *m*-nitrophenol is formed when phenol is mononitrated, as it can be, smoothly, by nitric acid in acetic acid. This conclusion is supported by the claim of Griffiths, Walkey, and Watson (*J.*, 1934, 631) that 1·4—2·2% of *m*-nitroanisole is formed in the mononitration of anisole by nitric acid of *d* 1·42, by nitric acid in sulphuric acid, nitric acid in acetic acid, nitric acid in acetic anhydride, and by benzoyl nitrate.

It seems improbable that strongly *op*-orienting groups like $^-$OH and $^-$OR could lead to appreciable *m*-nitration, when the weakly *op*-orienting halogens do not do so. This conclusion is reinforced by the consideration that the *op*-orienting property of $^-$OR groups, as of halogens, in aromatic substitution, is a tautomeric effect, and, unlike the inductive effect, is almost wholly a polarisability, therefore leading exclusively to *op*-substitution (Ingold and Shaw, *J.*, 1927, 2918).

Being engaged in a kinetic study of some of the special features of the mono-nitration of phenol and its derivatives we investigated these outstanding points concerning the orientation of nitration in these compounds.

Arnall and Griffiths, Walkey, and Watson based their conclusions on thermal analyses of the isolated nitration products; such methods may be unreliable unless by-products of mononitration can be removed more completely than can sometimes be established by ordinary analysis, however satisfactory apparently.

We have used three methods, applying one to phenol, one to anisole, and a third to both. These three methods give consistent results, disagreeing with those of the previous workers.

The first method, that of chromatographic adsorption, was applied to the product of the mononitration of phenol by nitric acid in acetic acid. It is possible to resolve mixtures of *o*-, *m*-, and *p*-nitrophenol by this method (cf. Strain, "Chromatographic Adsorption Analysis", Interscience Publishers, Inc., New York, 1942, p. 94); but, in application to the mononitration product of phenol, it was found that repeated adsorption of the various bands failed to reveal any trace of *m*-nitrophenol. This result, by itself, is not conclusive, as the method is difficult to standardise for small quantities of the *m*-compound, especially as the chromatogram is complicated by the presence of small amounts of derivatives of dihydroxydiphenylnitrogen oxide, which are formed during nitration of phenols.

The other method applied to phenol was an extension of Albert and Large's specific test for *m*-diamines (*Nature*, 1938, **142**, 435; Albert, *J.*, 1939, 920). They observed that *m*-diamines react with glycerol and oxalic acid in the presence of zinc or calcium chloride to give the fluorescent 2 : 8-diaminoacridine. By addition of stannous chloride to their reagent they extended the test to *m*-nitroamines and *m*-dinitro-compounds.

Our further extension of this test was to convert *m*-nitrophenol into *m*-nitroaniline by heating with amminozinc chloride and ammonium chloride. As the fluorescence of 2 : 8-diaminoacridine is quenched by phenols, any unconverted phenols were removed by extraction of the product from alkaline solution. No fluorescence was observed when this test was applied to the products of nitration of phenol by nitric acid in acetic acid, although when a trace of *m*-nitrophenol was first added to the nitration product a strong fluorescence was observed. Control experiments by this method established that the proportion of *m*-nitration under our conditions was less than 0·1%.

The first method to be applied to the nitration product of anisole was that of thermal analysis; but the fractionating column used in the removal of the non-isomeric by-products of mononitration was probably much more efficient than any at the disposal of earlier workers. We investigated this mononitration under several of the conditions used by Griffiths, Walkey, and Watson, *viz.*, nitration by nitric acid of *d* 1·42, by nitric acid in sulphuric acid, and by nitric acid in acetic acid. Two methods of thermal analysis were applied to each isolated product. One was a determination of the eutectic temperature, as the second arrest-point of the cooling curve. This temperature was always that of the binary mixture of *o*- and *p*-nitroanisoles to within our experimental error (about $\pm$ 0·1°). The other method involved

a determination of the clearing point, followed by similar determinations after additions of pure *o*-nitroanisole sufficient, first, to lower the clearing temperature in stages to the eutectic point, and then to raise it beyond that point. In each case, the composition–temperature curve thus traced coincided (to within the accuracy of the clearing point measurements: usually ± 0·3°), with the curve for binary mixtures of *o*- and *p*-nitroanisoles. This curve was first traced by Griffiths, Walkey, and Watson (*loc. cit.*), whose measurements we confirm. These determinations showed that the proportions of *m*-isomeride in our mononitration products could not have been more than a small fraction of 1%.

The second method applied to the mononitration products of anisole was the fluorescence test as described for the nitrophenols. Like *m*-nitrophenol, *m*-nitroanisole is converted into *m*-nitroaniline by heating with amminozinc chloride and ammonium chloride, and the product can be converted into 2 : 8-diaminoacridine by the method of Albert and Large. This test gave no detectable fluorescence when applied to the nitration products of anisole, although, as with phenol, a readily detectable fluorescence was obtained on the addition of small amounts of *m*-nitroanisole to the nitration product. Control experiments on these lines give an upper limit of 0·1% of *m*-nitration in the mononitration of anisole.

Thus it is proved by three independent methods that the proportions of *m*-isomeride formed in the mononitration of phenol and anisole are lower than we could detect, and very much lower than the proportions previously reported.

Experimental.

Materials.—Phenol was dried and distilled under reduced pressure in an all-glass apparatus. Anisole, alkali-washed and distilled, had b. p. 154—154·5°. The nitrophenols, from British Drug Houses, Ltd., were not further purified. The *m*- and *p*-nitroanisole, after crystallisation from aqueous alcohol, and the *o*-nitroanisole, prepared from steam-distilled *o*-nitrophenol and distilled, had m.p.s agreeing with those of Griffiths, Walkey, and Watson (here given in parentheses); *o*-, 10·4° (10·45°); *m*-, 35·7° (35·5°); *p*-, 52·1° (52·0°). Acetic acid was purified with chromium trioxide and fractionated. Nitric acid (95%) was distilled successively from 100% sulphuric acid and barium nitrate.

Miscellaneous Methods.—The initial content of the lower oxides of nitrogen in the nitrating mixtures was determined by the chloramine-T method (von Eck, *Pharm. Weekblad*, 1926, **63**, 1117; see also Minkoff, Thesis, London, 1945). The nitration of phenol by nitric acid in acetic acid was carried out with excess of phenol at 20°. The nitration products were poured into excess of alkali, and unchanged phenol was removed by treatment with carbon dioxide and ether. The mixture was just acidified with acetic acid, extracted with ether, and washed. The ether was removed, and the product dried in a vacuum desiccator. The nitrations of anisole by nitric acid (*d* 1·42), by nitric acid in sulphuric acid, and by nitric acid in acetic acid, were carried out essentially as described by Griffiths, Walkey, and Watson (*loc. cit.*). The products were extracted by ether from excess of alkali. Activated alumina was used for chromatographic adsorption; mixtures of ether and benzene were used as solvent, and in order to develop the chromatogram. Nitrophenols and nitroanisoles, either reference specimens or nitration products, were converted into nitroanilines by heating with amminozinc chloride (4 parts) and ammonium chloride (1 part) at 330° for 30 hours (cf. Menz and Muller, *Ber.*, 1886, **19**, 2916). The nitroanilines were then treated by the method of Albert and Large (*loc. cit.*). Cooling curves were determined in double-walled tubes, with stirring. Clearing points were determined in narrow, thin-walled tubes with stirring by a fine glass rod.

Examples of Thermal Analyses for the Nitration of Anisole.—(*a*) Anisole (0·95 g.-mol.) was treated with nitric acid (*d* 1·42; 1 g.-mol.) at 45° for 5 hours with continuous stirring. The product yielded the following data: Eutectic temperature from cooling curve, − 7·0°. Clearing point, + 23·3°. Deduced composition *o*-/(*o*- + *p*-) = 43·1% (Found: C, 55·9; H, 4·7; N, 9·1. Calc. for $C_7H_7O_3N$: C, 55·0; H, 4·8; N, 9·1%. Purity by $TiCl_3$ equivalent, 99·8%). Mixtures of the product with *o*-nitroanisole gave the following results:

Calc. % *o*- after addn.	43·1	65·0	69·8	80·0	84·5
Clearing point, calc.	(+23·3°)	+0·6°	−6·3°	−0·6°	+2·6°
,, ,, obs.	+23·3°	+0·9°	−6·1°	−0·4°	+2·3°

(*b*) Anisole (0·45 g.-mol.) was treated with a mixture of nitric acid (*d* 1·42; 0·5 g.-mol.) and sulphuric acid (0·5 g.-mol.) at 45° for 4 hours with continuous stirring. The product yielded the following data: Eutectic temperature from cooling curve, − 7·3°. Clearing point, + 26·2°. Deduced composition, *o*-/(*o*- + *p*-) = 39·8% (Found: C, 55·4; H, 4·5; N, 9·9%. Purity by $TiCl_3$ equivalent, 99·9%).

Calc. % *o*- after addn.	39·8	66·6	68·1	72·8	77·1
Clearing point, calc.	(+26·2°)	−1·9°	−4·0°	−5·4°	−2·4°
,, ,, obs.	+26·2°	−1·9°	−4·3°	−5·5°	−2·1°

(*c*) Anisole (0·05 g.-mol.) was treated with 200 c.c. of nitric acid (3M) in acetic acid at 20° for 12 hours, the initial concentration of nitrous acid being 0·03M. The product yielded the following data: Eutectic temperature from cooling curve, − 7·2°. Clearing point, + 33·0°. Deduced composition, *o*-/(*o*- + *p*-) = 30·5% (Found: C, 56·0; H, 4·8; N, 9·0%. Purity by $TiCl_3$ equivalent, 100·1%).

Calc. % *o*- after addn.	30·5	47·4	64·6	71·3	75·1	84·5
Clearing point, calc.	(+33·0°)	+20·2°	+1·5°	−6·4°	−3·8°	+2·0°
,, ,, obs.	+33·0°	+20·4°	+2·0°	−6·1°	−3·7°	+2·5°

(*d*) Anisole (0·05 g.-mol.) was treated with 200 c.c. of nitric acid (6·3M) in acetic acid at 20° for 15 hours, the initial concentration of nitrous acid being 0·12M. The product yielded the following data: Eutectic temperature from cooling curve, − 7·0°. Clearing point, + 30·4°. Deduced composition, *o*-/(*o*- + *p*-) = 34·0% (Found: C, 55·1; H, 4·7; N, 10·0%. Purity by $TiCl_3$ equivalent, 99·8%).

Calc. % *o*- after addn.	34·0	44·4	59·6	74·0	87·5
Clearing point, calc.	(+30·4°)	+22·7°	+7·6°	−4·5°	+3·8°
,, ,, obs.	+30·4°	+23·0°	+7·5°	−4·4°	+3·6°

Synthetic mixtures. (i) A mixture of *o*- and *p*-nitroanisole of composition *o*-/(*o*- + *p*-) = 69·3% gave the following results: Eutectic temperature, − 7·2° (Griffiths *et al.* give the same value). Clearing point, − 5·8° (interpolated from accepted values, − 5·7°). Clearing point after addition of 2·0% of *m*-nitroanisole, − 6·7°.

(ii) A mixture of *o*- and *p*-nitroanisole of composition *o*-/(*o*- + *p*-) = 81·8% gave the following results: Clearing point, + 0·9° (interpolated from accepted values, + 0·7°). Clearing point after addition of 1·5% of *m*-nitroanisole, + 0·6°.

Microanalyses were carried out by Drs. G. Weiler and F. B. Strauss of Oxford.

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NOTES.

1 : 9-*Diaminoacridine.* By (Miss) E. R. Klein and F. N. Lahey.

With the appearance of a paper by Albert, Rubbo, Goldacre, Davey, and Stone (*Brit. J. Exp. Path.*, 1945, **26**, 160) and one by Craig (*J.*, 1946, 534), in which reference was made to 1 : 9-diaminoacridine supplied by one of us, it becomes desirable to record the synthesis of this substance, although the work for which it was prepared has not yet been successfully concluded.

The synthesis was accomplished along standard lines. Condensation of 2-bromo-3-nitrobenzoic acid with *o*-nitroaniline in the presence of sodium carbonate without the use of a solvent gave 2 : 2′-dinitrodiphenylamine-6-carboxylic acid. The same product was obtained from 3-nitroanthranilic acid, *o*-bromonitrobenzene, and sodium carbonate with nitrobenzene as a solvent. Ring closure of 2 : 2′-dinitrodiphenylamine-6-carboxylic acid was accomplished with either sulphuric acid or phosphorus oxychloride yielding 1 : 9-dinitroacridone, which was readily reduced to 1 : 9-diaminoacridone by stannous chloride and hydrochloric acid or by sodium hydrosulphite. Reduction of 1 : 9-diaminoacridone with sodium amalgam gave 1 : 9-diaminoacridine directly, apparently without the intermediate formation of the acridan.

1 : 9-Diaminoacridine crystallises in yellow needles, m. p. 177°. It gives a colourless hydrochloride and is further characterised by the formation of an acetyl derivative, m. p. 250—251°.

2 : 2′-*Dinitrodiphenylamine-6-carboxylic Acid.*—(*a*) 2-Bromo-3-nitrobenzoic acid (5·0 g.), *o*-nitroaniline (5·0 g.), sodium carbonate (2·0 g.), and a trace of copper powder were thoroughly mixed and heated at 190—210° for 2 hours with stirring. On cooling, benzene was added, and the sodium salts were filtered off and taken up in hot water. On cooling this solution in ice, the sodium salt of 2 : 2′-dinitrodiphenylamine-6-carboxylic acid separated, and was filtered off and acidified with hydrochloric acid. 2 : 2′-*Dinitrodiphenylamine-6-carboxylic acid* crystallised from ethyl alcohol or xylene in yellow crystals, m. p. 246°. Yield, 1·2 g. (Found: N, 13·84. $C_{13}H_9O_6N_3$ requires N, 13·86%).

(*b*) A mixture of sodium 3-nitroanthranilate (4·1 g.), *o*-bromonitrobenzene (6·0 g.), sodium carbonate (1·06 g.), a trace of copper powder, and nitrobenzene (30 ml.) was refluxed for 4 hours. It was then poured into benzene and the precipitated sodium salts filtered off. The acid obtained on acidification was recrystallised from ethyl alcohol, and was identical with that recorded above. Yield, 1·6 g.

1 : 9-*Dinitroacridone.*—2 : 2′-Dinitrodiphenylamine-6-carboxylic acid (1·0 g.) and concentrated sulphuric acid (7 ml.) were heated on a steam-bath with stirring for 15 minutes. The dark green solution was then poured on ice. The precipitated 1 : 9-*dinitroacridone* was filtered off and heated with sodium carbonate solution and then with water. It crystallised from xylene in fluffy orange crystals, m. p. 257—258°. Yield, 0·7 g. (Found: C, 54·9; H, 2·6. $C_{13}H_7O_5N_3$ requires C, 54·7; H, 2·5%). The same compound was obtained by using phosphorus oxychloride for ring closure.

2 : 2′-Dinitrodiphenylamine-6-carboxylic acid (1·0 g.) was refluxed with phosphorus oxychloride (10 ml.) for 1 hour. The excess of phosphorus oxychloride was removed under reduced pressure and the dark residue treated with water and filtered off. The brown solid was boiled for 15 minutes with 5% hydrochloric acid and again filtered. It was then dissolved in boiling N/5-potassium hydroxide (50% alcohol). From this solution, 1 : 9-dinitroacridone was precipitated with dilute hydrochloric acid. Yield, 0·7 g.

1 : 9-*Diaminoacridone.*—Stannous chloride (2·5 g.) was dissolved in boiling concentrated hydrochloric acid (9 ml.) and the solution saturated with hydrogen chloride. 1 : 9-*Dinitroacridone* (1 g.) was added during 1 hour with stirring, and the boiling continued for half an hour after the addition was complete. The stannic chloride complex (1·8 g.) which settled out was filtered off, washed with ether and dissolved in 50 ml. of hot water. The solution was cooled in ice and a slight excess of ammonia (*d* 0·88) added.

The yellow precipitate was dried and extracted repeatedly with boiling absolute alcohol. Evaporation of the alcohol gave 1 : 9-*diaminoacridone* as greenish-yellow needles which did not melt up to 320°. Yield, 0·4 g. (Found : C, 68·7; H, 4·6. $C_{13}H_{11}ON_3$ requires C, 69·3; H, 4·9%).

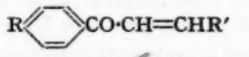
An easier method of reduction involved the use of sodium hydrosulphite. 1 : 9-Diaminoacridone (1·0 g.) was suspended in hot aqueous ethyl alcohol and sodium hydrosulphite added with constant stirring until a clear red solution was produced. A little hydrochloric acid was added and the solution boiled for ½ hour. Ammonia precipitated the 1 : 9-diaminoacridone. Yield, 0·5 g.

1 : 9-*Diaminoacridine*.—1 : 9-Diaminoacridone (0·3 g.) was suspended in 30 ml. of water at 80°. Sodium amalgam (5%; 12·0 g.) was added gradually over 2 hours with stirring, and heating continued for another 2 hours. After cooling, the precipitate was filtered off, washed with water, and crystallised from 30% alcohol. Yield, 0·22 g. 1 : 9-*Diaminoacridine* formed golden-yellow crystals, m. p. 177° (Found : C, 74·5; H, 5·3. $C_{13}H_{11}N_3$ requires C, 74·6; H, 5·3%). It gave a colourless solution in hydrochloric acid. Treatment with acetic anhydride and working up in the usual way gave a *diacetyl* derivative, m. p. 250—251° (Found : N, 14·5. $C_{17}H_{15}O_2N_3$ requires N, 14·2%).—UNIVERSITY OF MELBOURNE. [*Received, November 28th*, 1946.]

The Preparation and Bacteriostatic Action of Some Aminochalkones and Related Compounds.

By D. H. MARRIAN, P. B. RUSSELL, and A. R. TODD.

KUHN, MÖLLER, WENDT, and BEINERT (*Ber.*, 1942, **75**, 711) prepared a number of analogues of the sulphonamide drugs in which a *p*-aminobenzoyl group was substituted for the *p*-aminobenzenesulphonyl residue and showed that they possessed much weaker bacteriostatic properties than sulphanilamide. Later, however, Kuhn, Möller, and Wendt (*Ber.*, 1943, **76**, 405) showed that 4 : 4′-diaminobenzil has from two to six times the activity of sulphanilamide against *Staph. aureus*, and has accordingly about 30 times the activity of 4 : 4′-diaminobenzophenone. As an aspect of certain other investigations in this laboratory it seemed of interest to prepare and test some aminochalkones and related compounds of type (I), partly in view of the above findings and partly because of the presence of the grouping –C=C–CO– in a number of naturally occurring antibiotics.

(I.) 

4 : 4′-*Diaminochalkone* (I; R = NH_2; R′ = *p*-$NH_2{\cdot}C_6H_4$) was prepared by reduction of 4-amino-4′-nitrochalkone, itself obtained by hydrolysing *N* : ω-bis-*p*-nitrobenzylidene-*p*-aminoacetophenone (Scholtz and Huber, *Ber.*, 1904, **37**, 390). 4-Aminochalkone (I; R = H; R′ = *p*-$NH_2{\cdot}C_6H_4$) was prepared by reduction of the corresponding nitrochalkone with iron and acetic acid, and 4′-aminochalkone (I; R = NH_2; R′ = Ph) by hydrolysis of *N* : ω-dibenzylidene-*p*-aminoacetophenone. p-*Amino-ω-cinnamylideneacetophenone* (I; R = NH_2; R′ = CH:CH·C_6H_5) and p-*amino-ω-furfurylideneacetophenone* (I; R = NH_2; R′ = α-furyl) were prepared in similar fashion by hydrolysing the corresponding di-compounds.

The above compounds were tested against *Staph. aureus* and *Strept. hæmolyticus* by a serial dilution method in glucose broth and on a synthetic medium. Although all of them showed some activity (cf. Table) it was in no case of a high order. None showed any activity against *Esch. coli* or *Pseudomonas pyocyanea*.

	Maximum dilution inhibiting			
	Staph. aureus.		*Strept. hæmolyticus.*	
	Synthetic medium.	Glucose broth.	Synthetic medium.	Glucose broth.
4 : 4′-Diaminochalkone	1/10,000	—	1/100,000	1/10,000
4-Aminochalkone	1/5,000	—	1/50,000	1/5,000*
4′-Aminochalkone	1/10,000	—	1/10,000	—
I; R=NH_2; R′=CH:CHPh	—	—	1/5,000	1/5,000
I; R=NH_2; R′=α-furyl	1/10,000	1/5,000	1/5,000*	1/5,000

* Partial inhibition.

4-*Nitro*-4′-*aminochalkone*.—*N* : ω-bis-*p*-nitrobenzylidene-*p*-aminoacetophenone (3 g.; Scholtz and Huber, *loc. cit.*) was dissolved in ethanol (250 c.c.) and the solution acidified with dilute sulphuric acid. The precipitated sulphate was collected and dissolved in water, and the solution was made alkaline with sodium hydroxide. 4-*Nitro*-4′-*aminochalkone* (2·5 g.) separated as an orange-red microcrystalline powder; recrystallised from aqueous ethylene glycol monomethyl ether it had m. p. 220—221° (Found : C, 66·6; H, 4·6; N, 10·4. $C_{15}H_{12}O_3N_2$ requires C, 67·0; H, 4·5; N, 10·4%).

4 : 4′-*Diaminochalkone*.—4-Nitro-4′-aminochalkone (0·5 g.) was dissolved in acetic acid (6 c.c.) and the hot solution poured into a suspension of iron filings (2 g.) in dilute acetic acid (30 c.c. of 5%). The mixture was refluxed until all the nitro-compound had gone into solution, and then filtered hot. The filtrate, on cooling, deposited 4 : 4′-*diaminochalkone* as a crystalline powder. Recrystallised from ethanol the product formed orange needles (0·35 g.), m. p. 183—184° (Found : C, 75·5; H, 6·4; N, 11·5. $C_{15}H_{14}ON_2$ requires C, 75·5; H, 6·2; N, 11·8%); in pyridine solution it showed the blue fluorescence in ultra-violet light characteristic of 4-aminochalkones (Pfeiffer *et al.*, *Annalen*, 1925, **441**, 228), and on treatment with benzaldehyde it gave a *dibenzylidene* derivative, m. p. 180—181° (Found : N, 7·0. $C_{29}H_{22}ON_2$ requires N, 6·8%).

4′-*Aminochalkone*.—Prepared by treatment of *N* : ω-dibenzylidene-*p*-aminocetophenone with dilute sulphuric acid, 4-aminochalkone had m. p. 105—106°. Dilthey, Neuhaus, Reis, and Schommer (*J. pr. Chem.*, 1930, **124**, 81) give m. p. 108°.

4-*Aminochalkone*.—4-Nitrochalkone (Sorge, *Ber.*, 1902, **35**, 1068) (1 g.) was dissolved in hot acetic acid (3 c.c.) and added to a suspension of iron filings (2 g.) in dilute acetic acid (30 c.c. of 5%). The mixture was heated for 2 hours on the steam-bath, filtered, and cooled. The 4-aminochalkone which separated was recrystallised from aqueous ethanol, and thus obtained as deep yellow plates, m. p. 151—152°. Rupe and Porai-Koschitz (*Chem. Zentr.*, 1906, II, 1761), who prepared the substance by a different route, give m. p. 151°.

p-*Amino-ω-cinnamylideneacetophenone*.—*N* : ω-Dicinnamylidene-*p*-aminoacetophenone (Scholtz and Huber, *loc. cit.*) (3·6 g.) was dissolved in a mixture of ethanol (20 c.c.) and dilute sulphuric acid (5 c.c. of 2N), and the solution was heated on the steam-bath for 10 minutes and then cooled. The precipitated sulphate was collected and dissolved in water, and the solution was made alkaline with sodium hydroxide. The free *base* which separated was recrystallised from aqueous ethanol; it formed long yellow needles (2·1 g.; 83%), m. p. 159—160° (Found : C, 81·6; H, 6·3; N, 5·9. $C_{17}H_{15}ON$ requires C, 81·9; H, 6·2; N, 5·8%).

N : *ω-Difurfurylidene*-p-*aminoacetophenone*.—*p*-Aminoacetophenone (2·7 g.) and furfuraldehyde (3·85 g.) were dissolved in ethanol (25 c.c.), and cooled to 0°, a solution of potassium hydroxide (1·08 g.) in ethanol (20 c.c.) was added, and the mixture was allowed to stand overnight. The crystalline material which separated was recrystallised from ethanol. The *compound* formed yellow needles (4 g.), m. p. 103—104° (Found : C, 74·6; H, 4·4; N, 5·1. $C_{18}H_{13}O_3N$ requires C, 74·2; H, 4·5; N, 4·8%).

p-*Amino-ω-furfurylideneacetophenone*.—*N* : ω-Difurfurylidene-*p*-aminoacetophenone was hydrolysed with sulphuric acid in the normal manner (see above). Recrystallised from water, the *compound* formed yellow needles, m. p. 113—114° (Found : C, 72·9; H, 5·3; N, 6·6. $C_{13}H_{11}O_2N$ requires C, 73·2; H, 5·2; N, 6·7%).

The microbiological assays were carried out in the laboratories of Glaxo Laboratories Ltd., to whom our thanks are due. Grants from the Agricultural Research Council are gratefully acknowledged —
UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, December* 19*th*, 1946.]

Some New Condensation Products of Ethyl cyclo*Pentanone-2-carboxylate with Aromatic Amines.*

By H. C. BARANY and M. PIANKA.

FOR the formation of substituted anilides of *cyclo*pentanone-2-carboxylic acid a slight modification of the method of Blount, Perkin, and Plant (*J.*, 1929, 1983) was employed. 0·025 Mole of the amine was gradually added to 0·1 mole of boiling keto-ester containing 0·5 c.c. of pyridine. The mixture was boiled for 2 minutes, cooled, and allowed to crystallise. In some cases crystallisation set in only after some days. Crystals were filtered off, washed with cold ethanol, and treated with a 4% sodium hydroxide solution to free them from any anil formed. The solution was filtered and acidified with dilute acetic acid. The precipitate was filtered off, dried, and recrystallised from ethanol or amyl alcohol. The condensation *products* prepared are shown in the table opposite.

The condensation products were coupled in alkaline solution with phenyldiazonium chloride, yielding dyes insoluble in water, but soluble in lower alcohols, acetone, and ether, and ranging in colour from lemon-yellow to orange-red.

On application of the film strip test (Weissberger and Porter, *J. Amer. Chem. Soc.*, 1943, **65**, 1502), consisting of immersing an exposed strip of photographic film in a 3% sodium carbonate solution of equal weights of the anilide to be tested and *NN*-diethyl-*p*-phenylenediamine hydrochloride for 5 minutes, rinsing with water, and bleaching out the silver and silver halide, coloured strips ranging from greenish-yellow to light brown were obtained.

Mr. Edgerton and the Directors of Dufay-Chromex Limited are thanked for permission to publish this note and Mr. H. D. Murray and Mr. B. Gluck for suggesting the use of the anilides in colour photography.—RESEARCH LABORATORIES, DUFAY-CHROMEX LIMITED, ELSTREE, HERTS. [*Received, December* 9*th*, 1946.]

Amine.	M.p. of condensation product.	Formula.	Analysis. Found (%). C.	H.	N.	X.	Required (%). C.	H.	N.	X.
Aniline	104° *		—	—	—	—	—	—	—	—
Benzidine	charring >270 †		—	—	—	—	—	—	—	—
o-Toluidine	95— 96	$C_{13}H_{15}O_2N$	71·79	6·93	6·45	—	71·88	6·91	6·45	—
m-Toluidine	98— 99		71·83	6·98	6·45	—				
p-Toluidine	118—119		71·81	7·01	6·43	—				
p-Chloroaniline	115	$C_{13}H_{12}O_2NCl$	60·59	5·09	5·90	15·00	60·64	5·05	5·89	14·95
p-Bromoaniline	132	$C_{13}H_{12}O_2NBr$	50·96	4·31	4·98	28·71	51·09	4·26	4·96	28·34
2 : 4-Dichloroaniline	156	$C_{13}H_{11}O_2NCl_2$	52·90	4·06	5·12	25·97	52·94	4·04	5·15	26·10
2 : 5-Dichloroaniline	104		52·92	4·04	5·10	26·15				
o-Anisidine	155–156	$C_{13}H_{15}O_2N$	67·02	6·50	6·05	—	66·94	6·44	6·01	—
p-Anisidine	136–137		67·05	6·48	6·10	—				
2 : 5-Diethoxyaniline	95	$C_{16}H_{21}O_4N$	66·10	7·18	4·92	—	65·98	7·22	4·81	—
p-Aminoethyl benzoate	273—274	$C_{15}H_{17}O_4N$	65·56	6·09	5·14	—	65·46	6·18	5·09	—
α-Naphthylamine	162	$C_{16}H_{15}O_2N$	75·84	5·97	5·60	—	75·90	5·93	5·53	—
β-Naphthylamine	172		75·82	6·02	5·58	—				
NN-Diethyl-*p*-phenylenediamine	210—211	$C_{16}H_{22}O_2N_2$	70·02	8·07	10·32	—	70·06	8·05	10·22	—
o-Phenylenediamine	158—159	$C_{16}H_{20}O_4N_2$	65·69	6·10	8·63	—	65·86	6·09	8·54	—
m-Phenylenediamine	217—218 (decomp.)		65·76	6·11	8·65	—				
p-Phenylenediamine	200 (decomp.)		65·81	6·13	8·62	—				

Except for the condensation products of ethyl *cyclo*pentanone-2-carboxylate with *o*-, *m*-, and *p*-phenylenediamine, which were recrystallised from amyl alcohol, all the anilides were recrystallised from ethanol.

Melting points are uncorrected. X = halogen.

* Blount, Perkin, and Plant, *loc. cit.* † Linstead and Wang, *J.*, 1937, 807.

Some Applications of Surface Chemistry to Problems in Colloid Science.

THE TILDEN LECTURE, DELIVERED BEFORE THE CHEMICAL SOCIETY ON FEBRUARY 6TH, 1947, AND AT THE UNIVERSITY COLLEGE OF NOTTINGHAM ON MARCH 18TH, 1947.

By A. E. ALEXANDER, B.Sc., M.A., Ph.D.

SURFACE chemistry, or surface physical chemistry as it might more appropriately be termed, is concerned with the study of interfaces, generally those of macroscopic area. The field is now an extensive one and for that reason this lecture will be restricted to the three interfaces air–water, oil–water, and solid–liquid, which are of particular relevance to typical colloidal systems such as foams, emulsions, proteins, pastes, bacteria, etc. One important aspect, namely, reactions at interfaces, was surveyed by Professor Rideal in his recent Liversidge Lecture.[1]

In order to appreciate the results an outline of the principal experimental techniques, particularly those of more recent development, is desirable.

The study of insoluble monolayers at the air–water surface, based upon the classical work of Langmuir and of Adam, and later extended by Rideal, Harkins, and many others, undoubtedly forms the basis of our present knowledge of surface phenomena. The principal measured quantities of the monolayer are its surface pressure, Π ($\Pi = \gamma_{water} - \gamma_{film}$), its surface potential, ΔV ($\Delta V = V_{water} - V_{film}$), and its mechanical properties (viscosity and elasticity), all measured as a function of the molecular area (A).

Several techniques for the automatic recording of Π–A and ΔV–A curves have been devised;[2] these are particularly useful for examining phase changes and stability ranges in condensed monolayers. A simple film balance recently described[3] makes the accurate study of Π–A curves readily accessible.

Condensed monolayers on water can frequently be transferred to a solid surface by a simple dipping process, and layers many molecules thick have thus been built up. These "multilayers," or "built-up films" as they are termed, find a number of applications, particularly where very thin layers of known thickness are required.[4]

Oil–water interfaces are clearly more directly related to emulsion and biological systems than are air–water interfaces, but the study of insoluble monolayers there has proved much less amenable. However, accurate Π–A curves can now be measured by means of a technique based upon the ring method for surface tension.[5] Some studies of "interfacial potentials" (ΔV) and of the mechanical properties of such films have also been carried out.[6]

With adsorbed films at mobile interfaces recent interest has been largely concerned with the study of rates of adsorption and desorption. Slow changes can readily be followed by any of the standard methods for boundary tension; for rapid adsorptions the oscillating-jet method recently developed and extended to oil–water interfaces,[7] and a method utilising surface potentials,[8] are available.

As regards adsorbed films at the solid–liquid interface, mention may be made of a recent simple method for surface-area determination of fine powders. It merely involves using long-chain polar compounds, in organic media, as adsorbates, and determining the concentration before and after adsorption by spreading as a monolayer on a film balance.[9] The adsorption isotherm and the saturation uptake, giving the specific surface, are obtained in the usual manner, a value of 20 A.^{2} per long-chain molecule being assumed at the saturation point.

Having outlined the basic techniques, it is now possible to survey those results which bear directly upon a number of problems in colloidal systems.

The first problem considered will be the proteins, or rather certain aspects connected with them. In addition to their obvious biological importance proteins are common stabilising agents for foams and emulsions, an aspect discussed in more detail below.

Despite their solubility in water, proteins can usually be spread quantitatively as homogeneous monolayers at both air–water and oil–water interfaces. Such monolayers have been extensively studied in the hope of throwing some light upon the structure of the native protein molecule, as well as upon the formation and structure of protein membranes. In addition, attempts have been made recently to determine the molecular weight of proteins from Π–A curves of monolayers in the gaseous state.[10] The technique here is not simple, since measurements have to be made at very large areas and therefore at minute surface pressures. As an illustration of the method, egg albumin has given values of 40,000 [10] and 44,000,[11] close to the

accepted value for this protein in solution. In the case of hæmoglobin the " surface molecular weight " of 12,000 at the air–water interface indicates splitting into some five or six fragments (cf. results for hæmoglobin at an oil–water interface, mentioned below).

At the air–water interface the monolayers from widely different proteins are remarkably similar as regards their Π–A curves, although their viscosity and elasticity characteristics may vary considerably. Spreading appears to be accompanied by the complete loss of solubility and, in general, of enzymatic and specific immunological properties, indicating very radical and irreversible changes in structure. Such changes are believed to arise from the polypeptide chains in the protein molecule, originally coiled in some way so as to give a corpuscular form, being unrolled and reorientated on the surface by the action of the very asymmetric field at the interface. Other notable features are the ready formation of two-dimensional elastic gels showing marked hysteresis, and the ease of compression to areas (often less than 10 A.^{2} per residue) which appear too small for a close-packed monolayer. Oil–water interfaces of high interfacial tension show very similar phenomena, but as the tension is reduced the protein molecules appear to suffer less drastic changes (see also below).

Early speculations concerning the molecular structure of protein monolayers were not very conclusive, largely because of insufficient knowledge of the behaviour of linear polymers at interfaces, and of the bonding between the polar groups present, particularly between $>C{=}O$ and $H{-}N<$ in the main chain, and groups such as $-\overset{-}{C}OO$ and $\overset{+}{N}H_3$ in the side chains. A recent study [12] of monolayers of synthetic linear polymers of known structure (*e.g.*, poly-acrylates, poly-methacrylates, nylons, etc.) has enabled the contribution from the first of the above factors to be assessed much more precisely. Collapse of such films, and probably therefore of proteins too, leads to the formation of a thickened layer or overfilm rather than to a looping of the chains beneath the surface as previously believed by some workers. It may be mentioned that films built up by the multilayer technique from monolayers of amorphous polymers have been shown by electron diffraction to possess a much higher degree of order than those formed by the more usual methods.[13]

The interaction between the polar groups in proteins, in particular the extent of hydrogen bonding between the $>C{=}O$ and $H{-}N<$ groups of adjacent chains, has been investigated by comparing monolayers of simple paraffin-chain compounds containing the $-CO{\cdot}NH-$ group (*e.g.*, acetamides, ureas) with the analogous esters and ketones, where intermolecular hydrogen bonding is impossible.[14] The replacement of $-O-$ or $-CH_2-$ by $-NH-$ brings about striking changes in monolayer properties, and the conclusion is reached that intermolecular hydrogen bonding is certainly of major importance in protein monolayers. This approach enables reagents known to bring about changes in native proteins (*e.g.*, urea) to be assessed as regards their action upon the keto-imino-hydrogen bonds.

Turning now to two closely related classical colloidal systems, namely, foams and emulsions, the principal problems arising are as follows: the adsorption of the stabilising agent during the dispersion process, the structure of the adsorbed film and its importance in relation to the gross stability, and finally the desorption of stabilising agent as re-aggregation occurs. Surface chemistry has been able to supply considerable information about all of these problems, although it must be confessed that the picture is by no means complete.

The rate of adsorption at an air–water interface, which is usually followed by surface-tension measurements, is found to occur much more slowly than predicted by classical diffusion theory.[15] In the case of soaps and dyes, for example, the ratio of the calculated to the observed rate may be 10^6 or more. The hindrance to diffusion has usually been ascribed to an electrostatic potential barrier at the surface, arising from the presence of the adsorbed layer of long-chain ions, but the fact that similar anomalies arise with un-ionised compounds (*e.g.*, β-phenyl-propionic acid at pH 2) shows that this factor is certainly not the major one. The rate of attainment of equilibrium is accelerated by the presence of other surface-active substances, by insoluble monolayers, and by replacing the air by an oil phase.[8] Such experiments suggest that the main factor in these slow diffusions arises from the steric hindrance which a long hydrocarbon chain encounters when endeavouring to penetrate a comparatively close-packed monolayer. Anomalously slow adsorption of long-chain polar compounds can also occur from an oil phase to an aqueous interface, a phenomenon closely related to their well-known tendency to aggregate in organic media.[16]

Desorption, even with molecules of not particularly complex structure (*e.g.*, β-phenyl-propionic acid), appears to be an equally hindered process, although little has been done on this aspect, particularly at oil–water interfaces. Compression of a film adsorbed at an air–

water interface may even lead to the adsorbate separating out on the surface as a crystalline or liquid aggregate.[17]

The structure of the stabilising film in foams and emulsions, in particular whether the thickness is uni- or multi-molecular, can frequently be inferred indirectly from surface studies. In the case of water-soluble compounds (*e.g.*, soaps, and the lower fatty acids or alcohols) an equation of state can be deduced from the study of homologous longer-chain compounds which form insoluble monolayers, and this enables the adsorption, if confined to a monolayer, to be calculated at both oil–water and air–water interfaces.[17] The values thus calculated for the two most accurately studied compounds are seen from the data below to agree closely with the experimental ones obtained by McBain and his co-workers using the microtome method.

	Adsorption.	
Solute.	Calc.	Exptl.
β-Phenylpropionic acid	$8{\cdot}3 \times 10^{-8}$ g./cm.^{2}	$7{\cdot}7 \times 10^{-8}$ g./cm.^{2}
Laurylsulphonic acid	$5{\cdot}7 \times 10^{-10}$ g.-mol./cm.^{2}	$5{\cdot}2$—$5{\cdot}7 \times 10^{-10}$ g.-mol./cm.^{2}

The conclusion is therefore drawn that in foams, and by analogy also in emulsions (oil-in-water type), stabilised by water-soluble soaps, the interfacial films are no more than unimolecular in thickness, and are in a highly compressed gaseous (and hence fluid) state, with molecular areas of *ca.* 30 A.^{2} for simple straight paraffin-chain derivatives. Stabilisation arises chiefly from the marked reduction in the surface energy of the system, although other factors, particularly the surface viscosity of the adsorbed film, also play a part. The close connection between the lowering of interfacial tension and emulsion stability is shown particularly by systems stabilised by " interfacial complexes " formed between a water-soluble soap and organic compounds containing hydroxyl or amino-groups (*e.g.*, cholesterol, long-chain amines) dissolved in the oil phase.[18] The study of oil–water insoluble monolayers shows that in the case of stable oil-in-water emulsions the oil phase will be effectively displaced from the interface by the adsorbed monolayer of stabiliser.[5]

With the heavy-metal or oil-soluble soaps (*e.g.*, magnesium oleate) which stabilise the water-in-oil type of emulsion, the monolayers in equilibrium with the solid soap phase are also in a fluid, gaseous state, but the equilibrium spreading pressures are very much less than in the case of water-soluble soaps, which effectively rules out any stabilisation by a monolayer. The spontaneous formation of visible rigid films by reaction between heavy-metal cations and fatty acids at an oil–water interface indicates stabilisation by solid particles, in agreement with the observation that stable water-in-oil emulsions invariably contain solid soap.[19]

Protein solutions in contact with air–water and oil–water interfaces readily give rise to tough visible " skins ", a phenomenon first recorded by Ascherson over a century ago, and still very imperfectly understood. In the case of an air–water interface this " surface denaturation " continues until all the protein present has been removed as a coagulum practically devoid of surface activity. At oil–water interfaces, the rate and the extent of these surface changes diminish with decreasing interfacial tension.[20] For example, if hæmoglobin is desorbed (by changing the pH) from the surface of a fine emulsion stabilised by sodium cetyl sulphate its molecular weight is unaffected but its ultracentrifuge disymmetry coefficient has increased from 1·16 to 1·33, indicating some, but not complete, unfolding of the molecule.[21]

The behaviour of monolayers of proteins at air–water and oil–water interfaces suggests very strongly that proteins stabilise foams and emulsions by the formation of multimolecular films or skins rather than by a monolayer, these conferring mechanical protection.

The question of elasticity in adsorbed films is important in relation to the question of thermodynamic stability of foams and emulsions. Monolayers only show elasticity when in the condensed state, and from the study of equilibrium spreading pressures of crystals it would appear that all *condensed* monolayers are unstable with respect to their bulk phase. Accordingly, if an *adsorbed* film exhibits elasticity (as with protein or saponin solutions, and with heavy-metal soaps formed by metathesis at an interface), it would seem probable that its structures is multimolecular rather than unimolecular, and that the system is not in thermodynamic equilibrium.

Mention may be made in passing of Hardy's technique for studying foam stability by measuring the life-time of an air bubble liberated beneath an insoluble monolayer. Appreciable stabilisation is only obtained with coherent monolayers (expanded or condensed), and the stability decreases in the highly condensed state where the monolayers become unstable.[22]

Passing now to a consideration of pastes (concentrated dispersions of finely divided solids in a liquid continuum), some recent work [9] has shed much light upon the influence of surface-

active substances upon their macroscopic properties, such as flow behaviour and sedimentation volume. The adsorption upon polar powders such as sodium nitrate, using paraffin-chain compounds with different polar groups, in benzene or organic solution, was found to be in the following order $\cdot NO_2 > \cdot CO_2H > \cdot OH > \overset{|}{\underset{|}{C}}{=}O$. Parallel measurements of the coefficient of friction between large crystals showed that the friction was lowered in the same order. With increasing adsorption the ease of flow increases and the sedimentation volume decreases. Adsorption in these systems takes place with the polar groups of the adsorbate molecules oriented towards the polar surface of the crystal, and the hydrocarbon chains extending into the organic liquid. This outer surface of hydrocarbon reduces the interaction between the polar crystals and leads to the observed changes in macroscopic properties.

Finally, brief reference may be made to the application of surface studies to problems of a biological nature. Two examples only will be considered here, although others have been studied in this way (*e.g.*, the mechanism of fat absorption).[23]

Hexylresorcinol is a well-known anthelmintic for *Ascaris* and other intestinal worms. *In vitro* tests showed its activity to be considerably affected by the presence of bile salts or other soap-like substances, low concentrations generally producing some activation, but very high ones complete inhibition. Measurement of the surface activities of the various mixtures showed that the inhibition arises from the colloidal soap micelles, which form at the higher soap concentrations, competing with the biological surface for the fixed amount of drug.[24] The activation produced by low soap concentrations is related to the increased surface activity of the mixture, leading to an increased rate of penetration.

Similar conclusions have been found to apply to the bactericidal action of phenols in the presence of soaps. Rideal–Walker tests, and measurement of the rates of killing, show that the bactericidal activity increases up to the point where soap micelles start to form, and thereafter decreases.[25]

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OBITUARY NOTICE.

EDMUND BRYDGES RUDHALL PRIDEAUX.

1878—1946.

EDMUND BRYDGES RUDHALL PRIDEAUX was born in Barbados and educated at the Auckland Grammar School and Canterbury College, New Zealand University. His education, following the tradition of his family, was mainly classical; although he devoted himself to science he never lost his love of the classics and throughout his life would turn to them for solace and inspiration.

In 1901 he came to London but moved, in 1906, to the Heriot Watt College, Edinburgh, and thence, in 1909, to Liverpool University. Professor Donnan writes: "I had the great pleasure of welcoming Dr. E. B. R. Prideaux when he came to work in the Muspratt Laboratory of Physical and Electro-chemistry after having spent a year or two of research in the laboratory of Sir William Ramsay at University College, London. As a senior research worker of ability and experience he was a great source of strength to us in Liverpool and he made very valuable contributions to the research output of the laboratory. His lectures to the senior students on physico-chemical calculations were highly appreciated. I think I may claim the honour of having directed his attention to the special study of ionic equilibria in solutions and the various types of electrical potential differences associated therewith.

"Dr. Prideaux was a quiet, thoughtful, and scholarly man of science, and I have the happiest recollections of my association with him during those Liverpool years. He was one of a number of excellent men from New Zealand, including Denham, Stubbs, and Farrow, who contributed greatly to the success of the Muspratt Laboratory and the advance of physical chemistry."

In 1913 Prideaux moved to the Battersea Polytechnic and, in the following year, to the University College of Nottingham. His output of research was increasing rapidly but it received a check due to the outbreak of war. Much of his time was spent in assisting the National Shell-filling Factory at Chilwell and in preparative organic chemistry in connection with the production of β-eucaine. With the end of the war came the great influx of ex-service students, and in their interests he spent himself unstintingly.

Professor Kipping writes: "Dr. Prideaux was deeply imbued with the true scientific spirit which alone enabled him to accomplish the work for which he was distinguished in spite of his conscientious and painstaking preoccupation with his academic duties and, often also, with very inadequate apparatus.

"Although quiet and reserved in unfamiliar surroundings, with some of the attributes of a recluse, he was a kind and genial man and an interesting companion with broad and well informed views and decided opinions on many subjects. Some of the less desirable qualities which so often determine worldly success were, however, entirely foreign to his character; he was too altruistic, lacking in self-assertion and prone to neglect opportunities for his own advancement. It was, doubtless, for this reason that he failed to attain the higher rank in his profession to which he was entitled.

"He was not only, during many years, an accomplished member of my staff but also a highly valued friend."

As a research worker Prideaux was remarkable for his versatility; scarcely a single branch of chemistry escaped his attention, and he published some 90 papers in scientific journals apart from articles on scientific and educational topics. After obtaining the M.A. degree of New Zealand University he completed a research on Kauri resin and was awarded the B.Sc. degree. He continued to work on resins at the Imperial Institute in London in 1902, but then, under Ramsay, turned his attention to fluorine. He discovered the compounds BrF_3, TeF_6, and SeF_6. This work gained him the D.Sc. degree of London University. Fluorine continued to interest him throughout his life, and some 12 of his papers are devoted to this element and its compounds with selenium, tellurium, zirconium, and rubidium.

Phosphorus and its compounds also interested Prideaux, and his electronic formulation of phosphorus pentachloride received wide publicity. He published many papers on phosphoric and boric acids and was a pioneer in the use of modern indicators, and of the hydrogen and quinhydrone electrodes, and, in general, in the practical applications of the electrolytic dissociation theory. With A. T. Ward he devised the first "universal" buffer solution.

The dissociation constants of phenols and of alkaloids, the separation and estimation of pyridine and ammonia, the analysis of nitrotoluenes, benzoates, and salicylates, the spectro-

photometric examination of dyes and indicators, photo-synthetic phenomena in sea water, diffusion and membrane potentials, the corrosion of cement; these and other topics are evidence of the catholicity of Prideaux's tastes in research. In collaboration with F. O. Howitt he contributed valuable papers on the electrophoresis and isoelectric points of proteins and the kataphoresis of insulin. His theoretical papers helped the development of views on molecular structure.

Prideaux wrote several books: " The Theory and use of Indicators," " Problems in Physical Chemistry," and " A Survey of English Elementary Education." He was the author of the volume " Phosphorus " in Newton Friend's Text Book of Inorganic Chemistry, and joint author, with Herbert Lambourne, of the volume " Nitrogen," and with F. C. Laxton of " A Laboratory Course in Elementary Chemistry." He was, moreover, one of the pioneers in popular broadcast talks on scientific topics.

In 1908 Prideaux married the elder daughter of Rowland Bramwell, Esq., of Auckland, New Zealand. In 1946 he resigned his post as Reader in Physical and Inorganic Chemistry in the University College of Nottingham and, in recognition of his services, was awarded the title of *Lector Emeritus*. He then settled, with his wife and daughter, in his home at Canford Cliffs, Bournemouth, hoping to carry on his researches unhampered by the academic duties to which so much of his life had been devoted. The repose he had so richly earned by a life of labour was, however, denied him; he died on the 8th of May, 1946. His memory lives in the hearts of the students and friends who knew and valued him.

B. D. Shaw.

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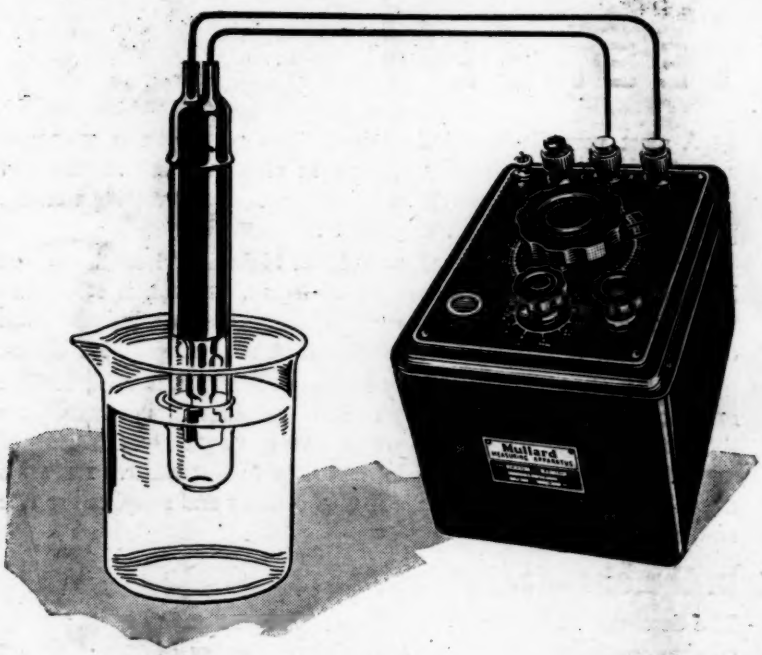

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